Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Chloral Hydrate's Impact on Brain Development: From Clinical Safety to Molecular Mechanisms

Pengyi Deng[1,*], Chenghao Zhu[1,*], Jie Zhang[1], Liling Zhu[1], Ting Xiao[2], Shuangquan Qu[1,2]

[1]The School of Pediatrics, Hengyang Medical School, University of South China (Hunan Children's Hospital), Changsha, Hunan, 410007, People's Republic of China; [2]Department of Anesthesiology, The Affiliated Children's Hospital of Xiangya School of Medicine, Central South University (Hunan Children's Hospital), Changsha, Hunan, 410007, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ting Xiao; Shuangquan Qu, Email irene_allen@163.com; shuangquanqu@126.com

Drug Design, Development and Therapy downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Chloral hydrate remains an irreplaceable first-line sedative in pediatric clinical practice, widely used for outpatient procedures and imaging examinations due to its proven efficacy and unique suitability for children. Despite its clinical indispensability, the impact of chloral hydrate on the developing central nervous system (CNS) in children remains largely unelucidated - a critical knowledge gap, given that children's immature blood-brain barrier (BBB) and high neuronal plasticity render their developing brains more vulnerable to pharmacological agents. Existing evidence demonstrates a significant negative correlation between the duration of chloral hydrate use and pediatric intelligence quotient (PIQ): longer usage is associated with lower PIQ scores. Prolonged use may impair non-verbal abilities reflected in PIQ, thereby compromising overall cognitive function - highlighting a critical clinical safety concern. By synthesizing current clinical observations and molecular mechanisms, this paper proposes that chloral hydrate may disrupt neurodevelopment through pathways including N-methyl-D-aspartate (NMDA) receptors, γ-aminobutyric acid (GABA) receptors, and the Mitogen-Activated Protein Kinase-Extracellular Signal-Regulated Kinase (MEK-ERK) signaling pathway. Basing on these findings, caution should be exercised regarding the use of chloral hydrate - particularly its long-term administration. Long-term follow-up of exposed children is recommended to continuously monitor cognitive function and neurodevelopment, with a focus on non-verbal abilities and overall intellectual development. Future research should prioritize prospective, long-term neurodevelopmental follow-up studies, specifically in children exposed to chloral hydrate, combined with neuroimaging and biomarker studies, to further explore its potential effects on neurodevelopment. In summary, this article synthesizes existing evidence to elucidate the effects of chloral hydrate on the developing brain, spanning clinical observations to underlying molecular mechanisms, with the aim of clarifying its potential implications for pediatric neurodevelopment.

Keywords: chloral hydrate, developing brain, neuronal apoptosis, outpatient sedation, pediatric

Introduction

Since the early 20th century, chloral hydrate has been widely used for pediatric sedation - particularly for outpatient sedation and imaging examinations[1,2] - and remains a dominant choice,[3–5] especially among neonates and infants.[6–8] Its enduring clinical role stems from practical advantages: rapid onset of action, ease of administration, favorable safety profile at standard doses, cost-effectiveness, and medical staff's familiarity with its use.

In recent years, newer sedatives have entered clinical practice, but monotherapy with these agents still fails to consistently meet the demands of outpatient pediatric examinations (eg, MRI). Such procedures require prolonged, stable sedation, yet newer drugs have notable limitations:[2] propofol carries a risk of respiratory depression, while dexmedetomidine struggles to achieve the sedation depth needed for complex procedures. For infants and low-birth-weight children uncooperative with intravenous puncture, chloral hydrate's oral/rectal administration minimizes procedural trauma; its 4–6-hour sedation duration also suffices for MRI/CT, supporting a high sedation success rate and making it indispensable in specific pediatric outpatient scenarios.[9,10]

Received: 28 August 2025
Accepted: 8 November 2025
Published: 15 November 2025

© 2025 Deng et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

However, despite its widespread use, chloral hydrate's safety and efficacy remain debated. While numerous studies confirm its significant sedative effects, concerns over potential risks have led some regions and experts to impose restrictions on its use in children. Notably, a decade-long analysis of chloral hydrate studies in PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) reveals its use is more prevalent in China than in other countries (Figure 1).

Critical gaps persist in understanding chloral hydrate's impact on pediatric brain development—a priority given the unique vulnerability of the developing brain: immature blood-brain barrier, heightened neuronal plasticity, and a sensitive metabolic system. Chloral hydrate's active metabolite, trichloroethanol, persists in the body for hours, amplifying potential neurodevelopmental risks. While prolonged exposure to anesthetic drugs is known to exacerbate neurocognitive damage, research on chloral hydrate remains limited: existing literature focuses primarily on its clinical sedative effects, with only preliminary exploration of its molecular mechanisms. Reviews on anesthetic neurotoxicity typically center on volatile inhalational anesthetics,[11–14] with scattered analyses of chloral hydrate—leaving no systematic integration of its pharmacological properties, pediatric clinical outcomes, and molecular pathways to inform judgments on neurodevelopmental risk.

Thus, studying chloral hydrate's impact on the developing brain and its underlying molecular mechanisms holds significant clinical value. This article synthesizes existing evidence to elaborate on these impacts, spanning clinical observations to molecular pathways, with the goal of clarifying its potential implications for pediatric neurodevelopment.

Pharmacological Properties and Pharmacokinetics of Chloral Hydrate

Drug Metabolism

Chloral hydrate is a classic sedative-hypnotic drug whose pharmacological activity primarily relies on its active metabolite, trichloroethanol (TCE) (Figure 2).[15–18] Its mechanism of action involves enhancing the activity of γ-aminobutyric acid (GABA) receptors in the central nervous system, thereby inducing sedative and hypnotic effects.[19] The drug has pharmacokinetic characteristics of rapid onset (within 30 minutes of administration) and short duration of action, making

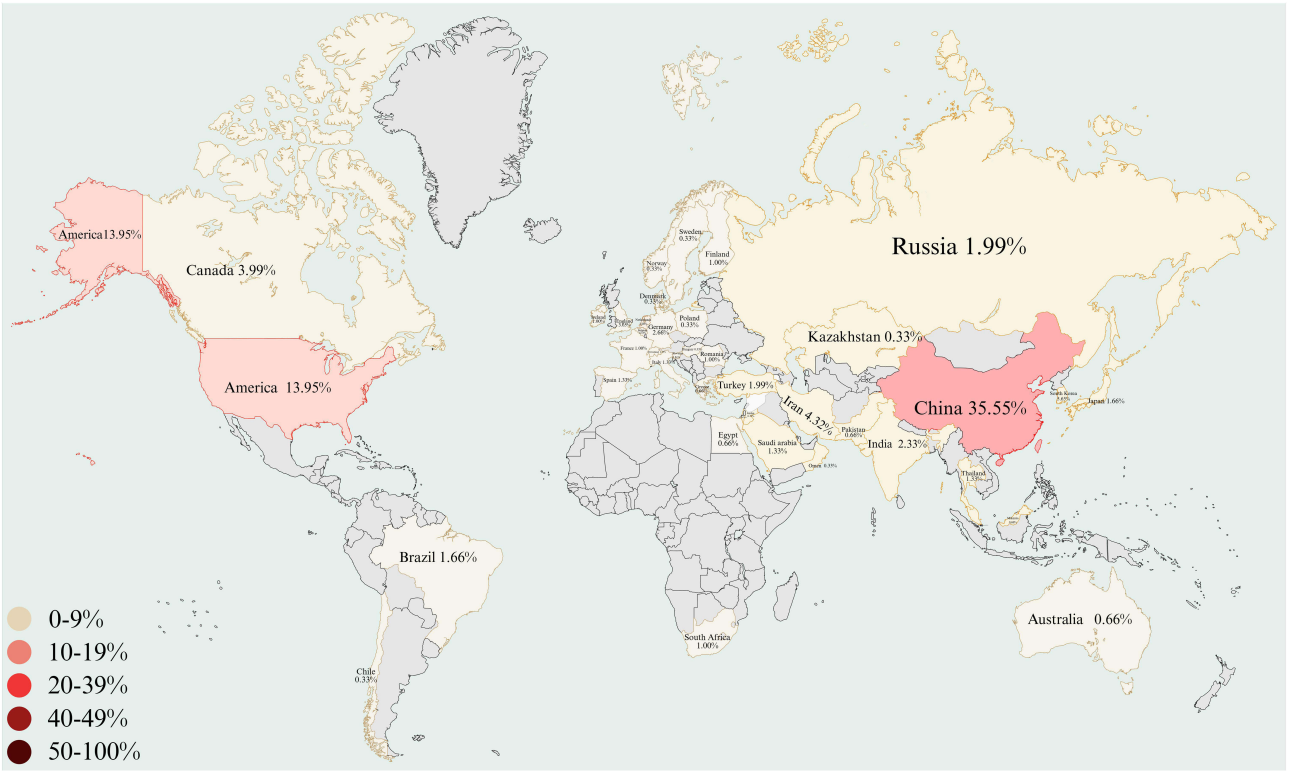

Figure 1 A map showing the distribution of chloral hydrate usage across different countries/regions. Based on a search of relevant studies on chloral hydrate in PubMed, Web of Science, and the China National Knowledge Infrastructure (CNKI) database over the past decade, this map shows the percentage of chloral hydrate usage across different countries and regions.

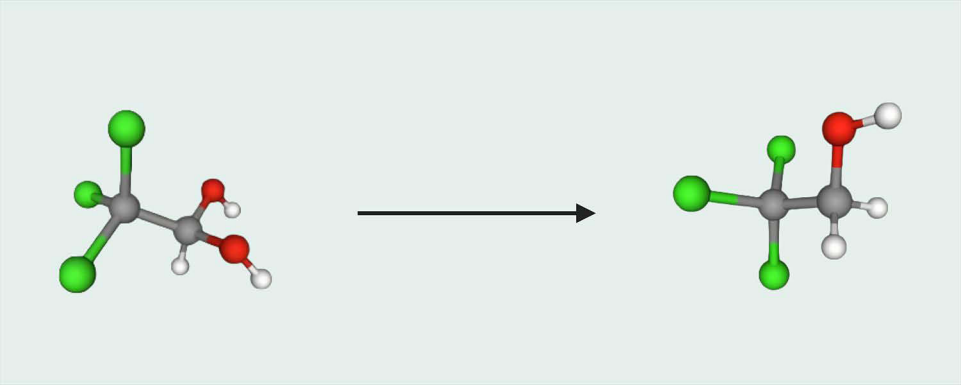

Figure 2 3D molecular reaction diagram showing the conversion of chloral hydrate (CH) to trichloroethanol (TCE). Chloral hydrate (left) is converted to trichloroethanol (right) under the catalysis of alcohol dehydrogenase.

it widely used in pediatric procedural sedation. In terms of metabolic pathways, chloral hydrate is primarily metabolized in the liver, where it undergoes extensive conversion catalyzed by alcohol dehydrogenase to form the active metabolite, TCE. TCE further undergoes conjugation with glucuronic acid to form an inactive conjugated metabolite, which is eventually excreted via the kidneys.[20] At therapeutic doses, the plasma half-life of TCE is 8–12 hours, while in cases of acute overdose, its half-life can extend to 35 hours. Additionally, TCE can undergo glucuronidation in the liver and further oxidation to form trichloroacetic acid (TCA), a metabolite whose elimination half-life exceeds 60 hours.[20]

It is noteworthy that the pharmacokinetic characteristics of chloral hydrate exhibit significant population differences, particularly in preterm infants and neonates. Due to the immature hepatic glucuronidation system in these populations, especially with insufficient activity of UDP-glucuronosyltransferase (UGT), the metabolism of TCE is impaired, leading to an extended half-life, resulting in notable pharmacokinetic alterations.[21–23] Other studies have confirmed that when a single oral dose of 50 mg/kg of chloral hydrate is administered, the pharmacokinetic profile in neonates significantly differs from that of adults. The half-life of TCE in preterm infants is approximately four times that of toddlers, while in full-term infants, it is about three times that of toddlers.[24] In toddlers, the TCE elimination half-life is similar to that of adults (8–10 hours), indicating mature hepatic metabolism.[25]

Dose-Effect Relationship

Before the 2000 revisions by the Agency for Sanitary Safety of Health Products (AFSSPS), chloral hydrate was the primary pediatric sedative for dental and podiatric procedures in the United States.[4,15] The potential risks associated with chloral hydrate, its use for adult anesthesia is no longer recommended according to contemporary guidelines. For pediatric procedural sedation, the initial oral dose ranges from 25 to 100 mg/kg, while rectal administration is limited to 50 mg/kg.[2] Considering the significant pharmacokinetic and pharmacodynamic differences across different age groups, clinical practice should involve age-stratified dosing plans for chloral hydrate sedation. This approach tailors the dose to match the physiological characteristics and pharmacokinetic properties of different age groups (such as neonates, infants, children, and adolescents), ensuring dose precision[1] (Table 1). Clinical validation results indicate that these dosing regimens demonstrate acceptable safety and efficacy in existing randomized controlled trials, providing a reliable basis for pediatric procedural sedation. This regimen shows acceptable safety and efficacy. At conventional doses, chloral hydrate has minimal effect on the respiratory center, but high doses may cause vasodilation, hypotension, and reduced myocardial contractility.[26,27]

The Short-Term and Long-Term Effects of Chloral Hydrate on Brain Development

Clinical Research Evidence

Chloral hydrate, a widely used sedative in clinical practice, has raised significant concerns regarding its use in pediatric populations. In neonates who received a single dose of chloral hydrate (30 mg/kg), the areas under the curve (AUC) for the P2

Table 1 Clinical Application of Chloral Hydrate in Different Age Groups

Age Group	Dose Range (mg/kg)	TCE t½ (h)	Sedation Success	Typical Settings	Side Effects
Preterm neonates[1,15,28,29]	25–50, 100 (Maximum dose within 24 hours)	37	95.7%	MRI, CT, Pulmonary Function Testing, BAEP	Respiratory depression and hypoxia, bradycardia, gastrointestinal discomfort, indirect hyperbilirubinemia, central nervous system depression, dependence and withdrawal symptoms.
Term neonates[1,15,30]	50–75	28	≈ 98%	MRI, CT, Pulmonary Function Testing, BAEP	Respiratory depression and hypoxia Bradycardia Gastrointestinal discomfort Allergic reactions Central nervous system depression, Metabolic acidosis.
Infants (28 d–23 m)[1,30,31]	50–80	28–40	83–100%	MRI, CT, ECG, ophthalmic examinations	Respiratory depression and hypoxia Bradycardia Gastrointestinal discomfort Allergic reactions Central nervous system depression, Metabolic acidosis.
Children (24 m–11 y)[1,31,32]	25–100	8 – 12	94–95%	MRI, CT; hearing tests; dental examinations; flexible bronchoscopy	Respiratory depression and hypoxia Bradycardia Gastrointestinal discomfort Allergic reactions Central nervous system depression, Metabolic acidosis.
Adolescents[1]	25–50	3–5	89.8%	Electrocardiogram and electroencephalogram examination.	Respiratory depression and hypoxia Bradycardia Gastrointestinal discomfort Allergic reactions Central nervous system depression, Metabolic acidosis.

Abbreviations: TCE, trichloroethanol (active metabolite of chloral hydrate); t½, elimination half-life; MRI, magnetic resonance imaging; CT, computed tomography; ECG, electrocardiography; BAEP, Brainstem Auditory Evoked Potential; d, days; m, months; y, years; REF, references; ≈, approximately.

and N2 components at the Fz and Cz electrode sites were significantly higher compared to a control group.[33] This suggests that even a single dose of chloral hydrate leads to increased neuronal activation, higher energy consumption, and decreased efficiency in processing auditory information. Additionally, this effect was associated with reduced sound discrimination and impaired information recognition, indicating that chloral hydrate may temporarily disrupt auditory perception—a cognitive function—in neonates, potentially delaying auditory development during a critical period.[33] A follow-up study of infants undergoing congenital heart surgery, with follow-up from surgery to 54 months, found a significant negative correlation between the duration of chloral hydrate use and performance IQ (PIQ). The 95% confidence interval for the association between the duration of chloral hydrate use and the decrease in PIQ was (−1.96, −0.10). Specifically, longer use of chloral hydrate was associated with a lower PIQ score, and increased use during the follow-up period may adversely affect the non-verbal abilities reflected in PIQ, thus impacting children's cognitive function.[34] This study suggests that long-term use of chloral hydrate may have adverse effects on neurodevelopment. While chloral hydrate has shown some efficacy in treating epilepsy, its impact on neurodevelopment in other clinical settings remains unclear. Future research should focus on evaluating the long-term effects of chloral hydrate in various clinical applications. Large-scale, multi-center clinical trials can systematically assess the impact of chloral hydrate on neurodevelopment in different populations.

Animal Experimental Evidence

A single conventional dose of chloral hydrate anesthesia reduced the surface expression of NMDA receptor subunit 1 (NR1) and subunit 2B (NR2B) on cortical neurons, while increasing their intracellular levels. The NMDA receptor is critical for neuronal survival through synaptic signaling, and its dysfunction can trigger apoptosis by disrupting calcium homeostasis and activating pro-apoptotic pathways.[18,35] Reduced surface expression of NMDA receptors at synaptic sites impairs signaling, disrupting normal neuronal function and promoting apoptosis. NMDA receptors are critical for synaptic plasticity, which is essential for maintaining synaptic efficacy and strength.[36] Chloral hydrate reduces NR2B subunit expression, potentially decreasing excitatory synapse efficacy, disrupting synaptic transmission, and impairing plasticity. This disruption of normal neuronal function impairs neurotransmission and metabolic processes, affecting

cognitive and motor functions. Chloral hydrate may induce hippocampal neuronal apoptosis in neonatal rats by activating Caspase-3, while also inhibits oxidative stress and lipid peroxidation,[37] interfering with normal neuronal function and leading to abnormal neurotransmission and metabolic abnormalities, which affect cognitive and motor functions. Chloral hydrate disrupts the MEK- ERK signaling cascade in the cerebral cortex by inhibiting ERK activation via phosphorylated MEK (p-MEK). This pathway is essential for memory formation and synaptic plasticity, and proper activation through phosphorylation is critical for maintaining neuroplasticity and neuronal function.[38] Chloral hydrate impairs MEK-ERK signaling, reduces p-ERK activity, disrupts neuronal function and neuroplasticity, and increases the risk of neurological abnormalities (Figure 3).

Notably, chloral hydrate pretreatment can exert neuroprotective effects in ischemic stroke by upregulating the expression of annexin A1 (ANXA1) and inhibiting neuroinflammation.[39] In the genetic absence epilepsy WAG/Rij rats, a dose of 175 mg/kg of intraperitoneal chloral hydrate significantly reduced the total number of spike-and-wave discharges (SWD), total spikes, and the overall duration of SWD. It not only rapidly suppressed seizure-like activity within 20 minutes of administration but also nearly completely abolished SWD over the next 80 minutes, without affecting the average duration of individual SWD. The mechanism of action is thought to be related to the enhancement of GABA receptor activity and the strengthening of central inhibitory effects to suppress neuronal hyperexcitability. This mechanism is consistent with the neuroprotective effects observed in other epilepsy models, where chloral hydrate regulates the central inhibitory neurotransmitter system to effectively control epileptic activity.[40] These findings provide a biological basis for understanding chloral hydrate's cerebral effects and highlight the need to study its long-term impacts.

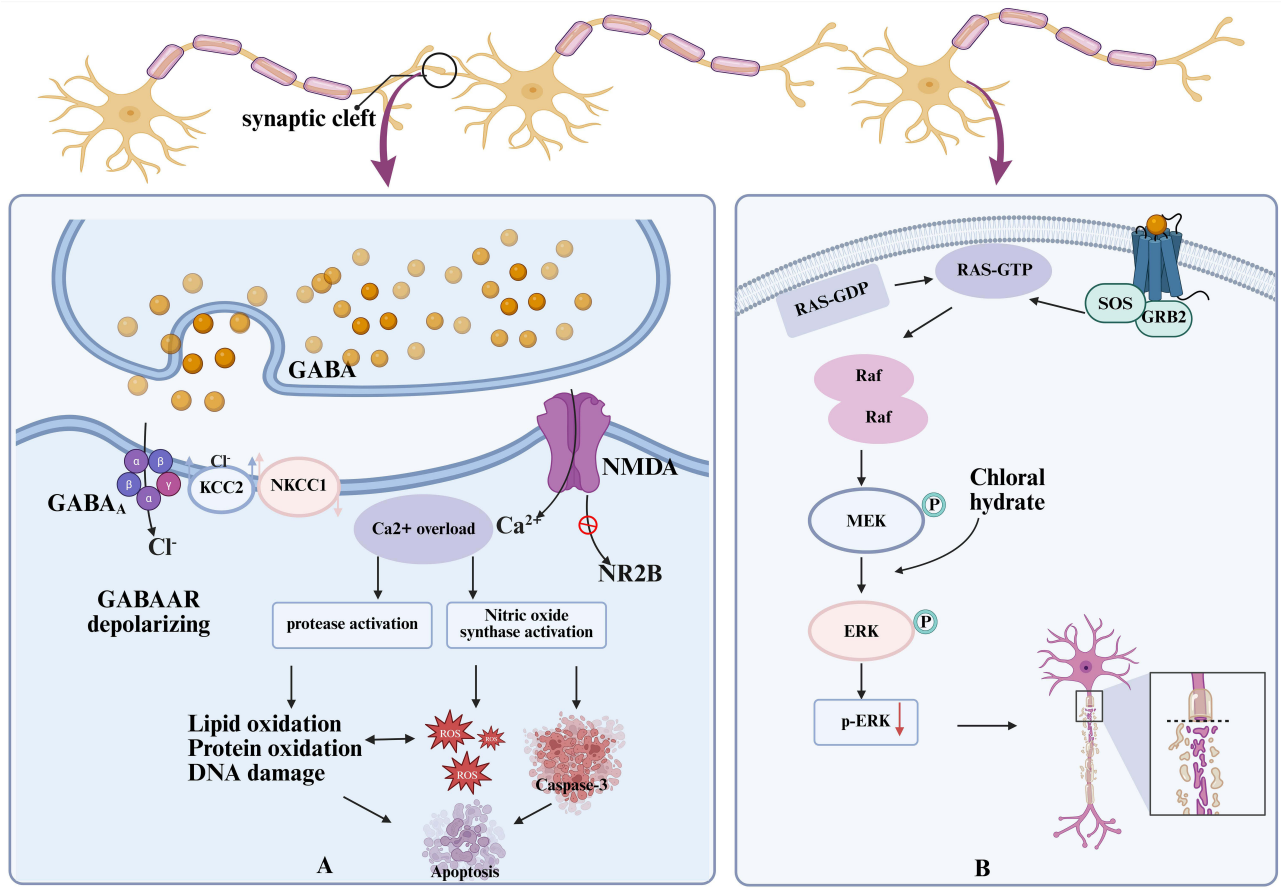

Figure 3 Schematic of molecular mechanisms for chloral hydrate-induced neurodevelopmental damage. This schematic outlines the key molecular pathways underlying chloral hydrate-induced neurodevelopmental damage. (**A**) shows: (1) $GABA_A$ receptor depolarization via imbalanced NKCC1/KCC2 ion transport; (2) NMDA/NR2B receptor downregulation (disrupting excitatory synaptic transmission/plasticity); and (3) NMDA receptor-mediated intracellular Ca2+overload—this activates proteases/nitric oxide synthase to generate excess ROS, which induce lipid peroxidation, protein oxidation, DNA damage, and Caspase-3-dependent neuronal apoptosis. (**B**) Illustrates chloral hydrate-inhibited MEK phosphorylation (reducing p-ERK), which disrupts the RAS-Raf-MEK-ERK cascade and impairs neuronal development/function. Collectively, dysregulated synaptic signaling and cell survival pathways mediate the neurodevelopmental damage.

https://doi.org/10.2147/DDDT.S563777

Mechanisms of Potential Toxicity

Molecular and Cellular Mechanisms

The neurotoxic mechanisms of chloral hydrate involve both molecular and cellular changes. Chloral hydrate disrupts the redox balance in the Human Monocytic Leukemia Cell Line 1 (THP-1), inducing oxidative stress and significantly increasing intracellular reactive oxygen species (ROS) production.[41] It also promotes the conversion of glutathione (GSH) to oxidized glutathione (GSSG), depleting intracellular antioxidants and increasing oxidative stress. Oxidative stress induces DNA double-strand breaks (DSBs), which activate the DNA damage-sensing mechanism. At DSB sites, H2A histone family member X (H2AX) is phosphorylated by DNA-dependent protein kinase (DNA-PK), forming γH2AX, a key marker of DNA damage.[42,43] If DNA damage is not repaired, it can lead to prolonged DNA damage response (DDR) activation, impairing neuronal function and potentially causing apoptosis or senescence.[41] Chloral hydrate can regulate oxidative stress responses in the THP-1 cell model. Based on this cellular-level research, we hypothesize that chloral hydrate may also induce oxidative stress in neuronal cells, leading to DNA double-strand breaks (DSBs) and ultimately causing neuronal cell damage. Through interactions with the immune system, chloral hydrate may activate oxidative stress pathways in neurons, inducing cell damage and apoptosis. This hypothesis is based on existing research on immune-neuronal interactions. Although specific literature in the nervous system is lacking, it can be inferred that oxidative stress may play an important role in this process, particularly in the context of neuronal damage.[44–46]

In the receptor-binding classification of common anesthetics and sedatives, chloral hydrate is classified as a γ-aminobutyric acid type A receptor (GABA-A) agonist.[47] γ-Aminobutyric acid (GABA), the principal inhibitory neurotransmitter, regulates neuronal excitability.[48,49] Chloral hydrate is metabolized in the liver to TCE, which binds to specific allosteric sites on the GABA-A receptor.[50] When GABA binds to the GABA-A receptor, it opens Cl^- channels, allowing chloride ions to enter neurons.[51–54] This hyperpolarizes the neuronal membrane, reducing excitability and suppressing activity.[49,50] During the rapid development of the fetal and neonatal brain, processes such as neurogenesis, migration, apoptosis, and synaptogenesis occur at elevated rates.[55] Chloral hydrate acts on GABA-A receptors and may disrupt these processes during development, potentially increasing neuronal apoptosis or causing abnormal synaptogenesis.[56] Currently, no comprehensive animal or clinical studies have explored the effects of chloral hydrate, particularly on fetal and neonatal brain development. Other GABA receptor agonists, such as volatile anesthetics and propofol, have shown adverse neurodevelopmental effects in animal studies.[19,57,58] As a GABA receptor binder, chloral hydrate is considered to carry similar risks.

Neurulation begins early in pregnancy, with neuronal migration occurring between 12 and 20 weeks of gestation. Neuroapoptosis continues from 24 weeks gestation to 4 weeks postnatally, while synaptic proliferation starts at 20 weeks, peaks between 1–2 years, and is followed by pruning,[59] myelination starts in the second trimester and continues throughout childhood.[60] The GABA and glutamate neurotransmitter systems are essential for neuronal connectivity and survival,[52] the developing brain is highly active and particularly sensitive to anesthetic and sedative drugs. As a pediatric sedative, chloral hydrate targets GABA receptors. Exposure to anesthetics acting on GABA or NMDA receptors increases neuronal apoptosis and causes long-term neurobehavioral changes.[61] During neurodevelopment, GABA receptor expression and function undergo significant changes. Excitatory signaling predominates early on, with GABA mediating cellular depolarization and calcium influx during the embryonic and early postnatal stages.[62] This is crucial for neuronal proliferation, migration, differentiation, and synaptic development. In the early stages of neuronal circuit formation, the excitatory action of GABA promotes progenitor cell proliferation and neuronal migration.[63,64] Sensory stimulation promotes the development of neuronal circuits, while sensory deprivation hinders it. GABA plays a crucial role in this process.[65,66] At birth, functional GABA synapses are present in the hippocampus of rodents, preceding the appearance of functional glutamatergic synapses, GABA-A receptors promote the development of glutamatergic synapses by modulating the NMDA receptor-mediated signaling pathway.[67] Excitatory GABA signaling is crucial for regulating synaptic plasticity, as well as the development and maturation of neurons. These processes are key to understanding various neurodevelopmental disorders.[53]

As the nervous system matures, GABA signaling gradually shifts from excitatory to inhibitory. This transition is regulated by the expression of GABA receptor subtypes, chloride ion concentration gradients, and associated cellular signaling pathways.[68] During neuronal maturation, the α1 subunit of GABA-A receptors gradually replaces the α3 subunit, enhancing the inhibitory efficacy of GABA signaling.[66]

Epigenetic Modifications

Epigenetics is a key field for studying gene expression regulation, involving mechanisms such as DNA methylation, histone modification, and non-coding RNAs.[69] As epigenetics becomes increasingly important in neurodevelopment, epigenetic changes are critical for neuronal differentiation, maturation, and function.[70,71] There is growing attention to the potential impact of chloral hydrate on epigenetic modifications during neurodevelopment.

DNA methylation, a key epigenetic modification, is recognized for its role in regulating neurodevelopment.[72] It involves the addition of methyl groups to cytosines, typically at cytosine-phosphate-guanine (CpG) dinucleotide sites, and plays a central role in gene expression regulation.[73] Methylation of CpG sites in promoter regions prevents transcription factor binding, inhibiting gene transcription and leading to gene silencing.[74] DNA methylation can also influence gene expression by modifying chromatin structure and altering gene accessibility. DNA methylation patterns undergo dynamic changes during development. In the early stages of embryonic development, extensive demethylation enables gene expression activation.[75] As development progresses, the methylation of specific genes stabilizes, creating distinct epigenetic marks.[76] During neurodevelopment, DNA methylation regulates processes such as neuron generation, migration, and synaptogenesis;[77] the expression of both brain-derived neurotrophic factor (BDNF) and synaptophysin (SYP) is regulated by DNA methylation. Increased methylation of the BDNF promoter reduces BDNF gene expression, establishing a inverse correlation between methylation and expression levels.[78] This regulatory mechanism is particularly evident under environmental stressors. Exposure to heavy metals or parental trauma can modify BDNF methylation,[79] impacting its expression and neurodevelopment in offspring. Changes in methylation patterns influence the binding of transcription factors to the promoters of BDNF and SYP, regulating their transcriptional activity.[80] The environmental toxin methylmercury (MeHg) also modifies DNA methylation, influencing BDNF and SYP expression. These findings underscore the critical role of epigenetic modifications, such as DNA methylation, in neurodevelopment and behavior, highlighting their importance in neurodevelopmental research.

Sensitivity of Special Populations

The BBB is underdeveloped in children, particularly in newborns and infants, whose BBB maturity is lower than that of adults, making it easier for drugs to cross,[81] this increased central nervous system sensitivity makes children more susceptible to the sedative effects of chloral hydrate, necessitating dose adjustments based on age and weight, with further modifications for special cases. The hepatic metabolic enzyme system is underdeveloped in children, particularly in newborns and preterm infants.[25] As liver enzyme synthesis and function are still developing, chloral hydrate metabolism in children is slower than in adults.[82] This metabolic deficiency may impair drug clearance, prolong its duration of action, and increase the risk of side effects. Children also exhibit significant differences in the volume of distribution relative to body surface area compared to adults. Their lower body weight, combined with a relatively larger body surface area, results in distinct drug distribution, influencing the efficacy and safety of chloral hydrate.[83] Therefore, developmental pharmacological factors must be carefully considered when administering chloral hydrate to ensure its safety and efficacy in children.

Chloral hydrate often shows greater efficacy than expected for pediatric outpatient sedation. When administered at low doses, it provides effective sedation while ensuring safety in children.[1,33] Children typically fall asleep quickly, with prolonged sleep duration, indicating heightened sensitivity to the drug. However, some may experience paradoxical excitation, influenced by individual variability, psychological state, and drug response, requiring careful monitoring. As children age, their respiratory systems mature, reducing the risk of respiratory depression. In contrast, neonates and infants are at higher risk of severe respiratory depression from sedatives like chloral hydrate due to their underdeveloped respiratory systems. Clinicians must carefully assess age and health status to ensure appropriate use and minimize respiratory risks.

Clinical Controversies and Alternative Approaches

Safety Controversy

Chloral hydrate, a traditional sedative, has been used in clinical practice for nearly a century. However, recent concerns about its safety and efficacy have arisen. The International Agency for Research on Cancer (IARC) has classified chloral hydrate as a Group 2A carcinogen (probably carcinogenic to humans). It induces liver tumors in male B6C3F1 mice, though no carcinogenicity was observed in male F344/N rats.[84] Current human studies have not established a definitive causal

relationship between chloral hydrate exposure and cancer risk, limitations like small sample sizes and low statistical power, the complete exclusion of its potential carcinogenic risk. In 2020, the Food and Drug Administration (FDA) updated its boxed warning, stating that repeated use of chloral hydrate may cause irreversible neurocognitive dysfunction in infants and young children. The exact mechanism remains unclear, heightened vigilance is necessary during its use. In clinical practice, even a single dose may lead to adverse reactions, including sedation failure and respiratory depression, with these effects being more pronounced in developmentally immature children.[33]

Comparison of Alternative Drugs

While chloral hydrate remains widely used for pediatric sedation, newer sedatives - including dexmedetomidine, propofol, and midazolam - are being explored as alternatives in select pediatric outpatient procedures. Though these agents deliver effective sedation in some scenarios, each has notable limitations that restrict their broader applicability. Dexmedetomidine acts primarily on α2-adrenergic receptors,[85] inducing sedation by inhibiting norepinephrine release and causing minimal respiratory depression.[86] However, dexmedetomidine, when used alone in pediatric outpatient settings, is insufficient to achieve sedation.[87] Propofol targets GABA and NMDA receptors, providing rapid onset and recovery, but its suppressive effects on the respiratory and cardiovascular systems introduce risks for specific pediatric groups.[88,89] Midazolam exerts sedation via GABA receptors, yet it carries a higher risk of nausea, vomiting, and delirium compared to chloral hydrate, limiting its use in certain outpatient surgeries.[90,91] Ketamine, as an NMDA receptor antagonist, has various administration routes, rapid onset and recovery, and preserves airway reflexes. However, it may induce side effects such as hallucinations, emergence delirium, and involuntary limb movements. It is often used in combination with other drugs to mitigate these side effects and enhance the sedative effect.[92,93] By contrast, chloral hydrate retains its importance in pediatric outpatient sedation due to key advantages over these alternatives: reliable efficacy, favorable safety profile at standard doses, cost-effectiveness, and ease of administration. These benefits are particularly pronounced in neonates and infants, where it demonstrates distinct clinical value. Thus, chloral hydrate remains the drug of choice in many medical institutions, especially when other sedatives are unsuitable (Table 2).

Table 2 Chloral Hydrate vs Alternative Sedatives

Drug	Dose & Route	Onset	Duration	Clinical Context	Sedation Success	Limitation
Chloral Hydrate[1,10,15,94]	PO 25–100 mg/kg Enema 25–100 mg/kg	30–60 min	60–120 min	Moderate to deep sedation for pediatric outpatient imaging (MRI/CT), EEG/ECG, ophthalmic and hearing exams; ideal when IV access is difficult	94%	Respiratory depression at higher doses
Dexmedetomidine[1,10,95–97]	IN 2.5–3 μg/kg IV 1–3 μg/kg	IN 20–30 min IV 5–10 min	IN 30–45 min IV 30–70 min	Moderate sedation for noninvasive procedures (MRI, EEG, echocardiography); commonly used as adjunct to other sedatives	62%	Slow onset; bradycardia
Midazolam[1,10,95]	PO 0.25–0.50 mg/kg IV ≤5 y 0.05–0.10 mg/kg; 6–12 y 0.025–0.050 mg/kg; >12 y 1–2 mg	PO 20–30 min IV 3–5 min	PO 30–60 min IV 30–45 min	Moderate sedation for dental procedures, minor surgeries, and imaging; or pre-procedure anxiolysis	36%	Unable to achieve deep sedation when used alone; paradoxical excitement or delirium
Propofol[1,98–101]	IV 1–2 mg/kg	≤0.5 min	5–15 min	Deep sedation for short procedures requiring complete immobility (eg, MRI, CT, gastroscopy, colonoscopy) outside OR; rapid recovery	97–99%	Respiratory depression
Ketamine[100–103]	PO 5–6 mg/kg IN 5–10 mg/kg IM 4–5 mg/kg IV 0.5–2 mg/kg	PO 20–30 min IN 5–10 min IM 3–5 min IV 1–2 min	PO 60–120 min IN 10–60 min IM 30–60 min IV 10–15 min	Moderate deep sedation with analgesia for painful or immobilizing procedures (eg, fracture reduction, laceration repair, burn care)	93–36%	Emergence phenomena (eg, hallucinations, agitation); motion artifacts during imaging

Abbreviations: PO, oral; IN, intranasal; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; CT, computed tomography; ECG, electrocardiography; EEG, electroencephalography; OR, operating room; y, year(s); m, minute(s); eg, for example.

Research Gaps and Future Directions

Clinical Study Design

In recent years, chloral hydrate has attracted increasing attention as an outpatient sedative for children. A prospective cohort study lasting 5 to 10 years could track the neurodevelopmental trajectory of children exposed to chloral hydrate, systematically monitoring developmental changes at various time points and providing valuable data for clinical practice. The study should compare children exposed to chloral hydrate after birth with those who were not, to explore its long-term effects on the pediatric nervous system. During long-term follow-up, standardized neuropsychological assessment tools, such as the Wechsler Intelligence Scale, should be used to regularly evaluate cognitive function and behavioral performance, enhancing the credibility of the findings.[104,105] Neuroimaging techniques, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), should be employed to assess the impact of chloral hydrate on brain structure and function, exploring changes in neural networks. These technologies will help elucidate the potential mechanisms of chloral hydrate in neurodevelopment and provide comprehensive data to support clinical applications. Long-term cohort studies will reveal the lasting effects of the drug, providing scientific evidence for its safe clinical use.

Dose-gradient experimental design is a key method for investigating the neurotoxicity of chloral hydrate, particularly for exploring its toxicity threshold. This experiment typically involves groups of children exposed to varying doses of chloral hydrate, with the dosage gradually increasing while systematically assessing neurological responses to identify the dose range at which neurological dysfunction occurs. This provides essential safety dose guidelines for clinical use. Electrophysiological techniques, such as multi-channel recording and patch-clamp, are used to monitor neuronal electrical activity in real time, evaluate the effects of different doses of chloral hydrate on neuronal excitability and synaptic transmission, and construct a dose-response model to analyze its impact. Dose-gradient experiments help define the threshold effects of chloral hydrate on neuronal apoptosis, synaptic plasticity, and other neurological functions, thus establishing the safe exposure limits. By combining animal studies and clinical research, the impact of various doses on the nervous system can be assessed, with measurements of neuronal survival, apoptosis markers, and other factors to explore the toxicity threshold of chloral hydrate. These experiments support the advancement of precision medicine by ensuring that clinical dosing better meets individual needs and providing scientific evidence for the safe use of medications in children.

Precise Medical Applications of Chloral Hydrate

Personalized medication strategies are receiving increasing attention in clinical practice, particularly regarding the use of chloral hydrate as a sedative-hypnotic for children. Precision medicine emphasizes tailoring treatment plans based on a patient's genetic background, environmental factors, and lifestyle, which is particularly significant for the application of chloral hydrate. Pharmacogenomics and biomarker research can help better understand the metabolic mechanisms and potential neurotoxicity of chloral hydrate, optimize drug regimens, reduce adverse reactions, and improve therapeutic outcomes.[106]

Conclusions

In summary, current studies have not identified significant neurodevelopmental harm caused by standardized short-term use of chloral hydrate. It is important to note that although chloral hydrate has shown neuroprotective effects in animal models of brain injury, epilepsy, and other disease states, systematic studies on its long-term effects are still lacking, and whether prolonged or repeated use induces developmental neurotoxicity remains unaddressed—representing a critical gap in understanding its impact on the developing brain.

Chloral hydrate exerts its sedative effect by activating GABA receptors, while downregulating NMDA/NR2B receptors, leading to excessive ROS generation, inducing Ca^{2}+ overload and DNA damage, inhibiting the MEK-ERK pathway, and activating the caspase-3-dependent apoptosis pathway, ultimately resulting in neuronal apoptosis. These mechanisms are based on published evidence and existing hypotheses, providing a theoretical framework for ongoing research, clarifying future research directions, and supporting the biological plausibility of chloral hydrate's potential neurodevelopmental effects. Although it is known that the density of NMDA and GABA receptors changes with age and affects neurodevelopment,[107,108] no studies have yet explored whether chloral hydrate influences neurodevelopment by

altering receptor density. Future research should involve age stratification to better understand the potential impact of chloral hydrate on the developing brain at different stages.

In clinical practice, there is currently a lack of long-term follow-up studies on pediatric populations exposed to chloral hydrate. Future research should prioritize prospective, long-term neurodevelopmental follow-up studies—specifically in pediatric populations exposed to chloral hydrate—to clarify its long-term effects on neurocognitive function and brain development. Integrating neuroimaging (to assess structural/functional brain changes) and biomarker research (to validate key molecular pathways) will further deepen understanding of chloral hydrate's mechanism of action, providing evidence to develop safer, more personalized pediatric sedation protocols.

Thus, through multidisciplinary collaboration and advances in precision medicine, progress can be made in optimizing the safety and efficacy of pediatric sedation—ultimately enhancing the quality of pediatric medical care and addressing unresolved concerns about chloral hydrate's role in neurodevelopment.

Abbreviation

CNS, central nervous system; BBB, blood brain barrier; CNKI, China National Knowledge Infrastructure; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; MEK, Mitogen-Activated Protein Kinase; ERK, Extracellular Signal-Regulated Kinase; TCE, Trichloroethanol; AFSSPS, Agency for Sanitary Safety of Health Products; AUC, areas under the curve; PIQ, Performance Intelligence Quotient; NR1, N-methyl-D-aspartate receptor subunit 1; NR2B, N-methyl-D-aspartate receptor subunit 2B; p-MEK, phosphorylated MEK; THP-1, Human Monocytic Leukemia Cell Line 1; ROS, reactive oxygen species; GSH, glutathione; GSSG, oxidized glutathione; DSBs, DNA double-strand breaks; DNA-PK, DNA-dependent protein kinase; H2AX, H2A Histone Family Member X; DSB, Double-Strand Break; PAC, Proton-Activated Chloride Channel; γH2AX, gamma-H2A histone family member X; DDR, DNA damage response; GSH-Px, glutathione peroxidase; GABA-A, γ-aminobutyric acid type A receptor; CpG, cytosine-phosphate-Guanine; BDNF, rain-derived neurotrophic factor; SYP, synaptophysin; MeHg, methylmercury; IARC, International Agency for Research on Cancer; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; IPSCs, induced pluripotent stem cells; FDA, Food and Drug Administration.

Acknowledgment

The authors are particularly grateful to Professor Davidson, Head of Anaesthesia Research at Murdoch Children's Research Institute (MCRI), for his academic guidance, whose expertise has been invaluable to this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Hunan Provincial Natural Science Foundation of China (Grant No. 2024JJ5220) and the Chinese Youth Medical Innovation Research Project.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Chen Z, Lin M, Huang Z, et al. Efficacy of chloral hydrate oral solution for sedation in pediatrics: a systematic review and meta-analysis. *Drug Des Devel Ther*. 2019;13:2643–2653. doi:10.2147/DDDT.S201820
2. Fong CY, Tay CG, Ong LC, Lai NM. Chloral hydrate as a sedating agent for neurodiagnostic procedures in children (review). *Cochrane Database Syst Rev*. 2017. doi:10.1002/14651858.CD011786.pub2

3. Karaoui M, Varadaraj V, Munoz B, et al. Chloral hydrate administered by a dedicated sedation service can be used safely and effectively for pediatric ophthalmic examination. *Am J Ophthalmol*. 2018;192:39–46. doi:10.1016/j.ajo.2018.05.003
4. Mataftsi A, Malamaki P, Prousali E, et al. Safety and efficacy of chloral hydrate for procedural sedation in paediatric ophthalmology: a systematic review and meta-analysis. *Br J Ophthalmol*. 2017;101(10):1423–1430. doi:10.1136/bjophthalmol-2016-309449
5. Chen ML, Chen Q, Xu F, Zhang JX, Su XY, Tu XZ. Safety and efficacy of chloral hydrate for conscious sedation of infants in the pediatric cardiovascular intensive care unit. *Medicine*. 2017;96(1):e5842. doi:10.1097/MD.0000000000005842
6. Chen Z, Qin F, Zeng L, Zhang L. Efficacy and safety of rectal chloral hydrate for pediatric procedural sedation: a systematic review and meta-analysis. *Medicine*. 2024;103(35):e39403. doi:10.1097/MD.0000000000039403
7. Jang YE, Joo EY, Park JB, et al. Comparison of combined intranasal dexmedetomidine and ketamine versus chloral hydrate for pediatric procedural sedation: a randomized controlled trial. *Korean J Anesthesiol*. 2025;78(3):248–260. doi:10.4097/kja.24815
8. Yanling D, Lijuan Y, Yingxin M, Dewu Z. The application of sleep deprivation combined with chloral hydrate on pediatric dermatological surgery. *Dermatol Surg*. 2025;51(4):380–382. doi:10.1097/DSS.0000000000004497
9. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm*. 2016;7(2):27–31. doi:10.4103/0976-0105.177703
10. De Rover I, Wylleman J, Dogger JJ, Bramer WM, Hoeks SE, De Graaff JC. Needle-free pharmacological sedation techniques in paediatric patients for imaging procedures: a systematic review and meta-analysis. *Br J Anaesth*. 2023;130(1):51–73. doi:10.1016/j.bja.2022.09.007
11. Jevtovic-Todorovic V. Anaesthesia-induced developmental neurotoxicity: reality or fiction? *Br J Anaesth*. 2017;119(3):455–457. doi:10.1093/bja/aex161
12. Creeley CE, Dikranian KT, Dissen GA, Back SA, Olney JW, Brambrink AM. Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. *Anesthesiology*. 2014;120(3):626–638. doi:10.1097/ALN.0000000000000037
13. Istaphanous GK, Howard J, Nan X, et al. Comparison of the neuroapoptotic properties of equipotent anesthetic concentrations of desflurane, isoflurane, or sevoflurane in neonatal mice. *Anesthesiology*. 2011;114(3):578–587. doi:10.1097/ALN.0b013e3182084a70
14. Sasaki russell JM, Chinn GA, Maharjan D, Eichbaum Y, Sall JW. Female rats are more vulnerable to lasting cognitive impairment after isoflurane exposure on postnatal day 4 than 7. *Br J Anaesth*. 2019;122(4):490–499. doi:10.1016/j.bja.2018.12.008
15. Ratnapalan S. Chloral hydrate sedation in children. *Clin Pediatr*. 2014;53(10):933–936. doi:10.1177/0009922813508000
16. Köles L, Wirkner K, Fürst S, Wnendt S, Illes P. Trichloroethanol inhibits ATP-induced membrane currents in cultured HEK 293-hP2X3 cells. *Eur J Pharmacol*. 2000;409(3):R3–5. doi:10.1016/s0014-2999(00)00833-5
17. Kiametis AS, Stock L, Cirqueira L, Treptow W. Atomistic model for simulations of the sedative hypnotic drug 2,2,2-trichloroethanol. *ACS Omega*. 2018;3(11):15916–15923. doi:10.1021/acsomega.8b02017
18. LacKamp A, Zhang GC, Mao LM, Fibuch EE, Wang JQ. Loss of surface N-methyl-d-aspartate receptor proteins in mouse cortical neurones during anaesthesia induced by chloral hydrate in vivo. *Br J Anaesth*. 2009;102(4):515–522. doi:10.1093/bja/aep009
19. McCann ME, Soriano SG. Does general anesthesia affect neurodevelopment in infants and children? *BMJ*. 2019;367:l6459. doi:10.1136/bmj.l6459
20. Abbas RR, Seckel CS, Kidney JK, Fisher JW. Pharmacokinetic analysis of chloral hydrate and its metabolism in B6C3F1 mice. *Drug Metab Dispos*. 1996;24(12):1340–1346.
21. Bus JS. Toxicity and metabolism studies of chloral hydrate. *Toxicity Report Series*. (59).
22. Yueh MF, Chen S, Nguyen N, Tukey RH. Developmental, genetic, dietary, and xenobiotic influences on neonatal hyperbilirubinemia. *Mol Pharmacol*. 2017;91(5):545–553. doi:10.1124/mol.116.107524
23. Buyssens L, Valenzuela A, Prims S, et al. Ontogeny of CYP3A and UGT activity in preterm piglets: a translational model for drug metabolism in preterm newborns. *Front Pharmacol*. 2023;14:1177541. doi:10.3389/fphar.2023.1177541
24. Mayersa DJ, Hindmarsh KW, Sankaranb K, Góreckia DKJ, Kasianb GF. Chloral hydrate disposition following single-dose administration to critically ill neonates and children. *Devel Pharmacol Ther*. 1991;16(2):71–77.
25. Verscheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM. Physiologically-based pharmacokinetic models for children: starting to reach maturation? *Pharmacol Ther*. 2020;211:107541. doi:10.1016/j.pharmthera.2020.107541
26. Paparella SF. Chloral hydrate: safety risks still worth mentioning. *J Emerg Nurs*. 2018;44(1):81–83. doi:10.1016/j.jen.2017.09.002
27. Gauillard J, Cheref S, Vacheron Trystram M-N, Martin J-C. L'hydrate de chloral, un hypnotique à oublier [Chloral hydrate a hypnotic best forgotten]. *L'Encephale*. 2002;XXVIII(1):200–204.
28. Jang YE, Park JB, Kang P, et al. Risk factors for chloral hydrate sedation failure in pediatric patients: a retrospective analysis. *Korean J Anesthesiol*. 2024;77(5):526–536. doi:10.4097/kja.24125
29. Lee J, Youn YA, Kim SJ, et al. Adverse effects of chloral hydrate in neonates: frequency and related factors. *J Korean Soc Neonatol*. 2011;18(1):130. doi:10.5385/jksn.2011.18.1.130
30. Wandalsen GF, Lanza FDC, Nogueira MCP, Solé D. Efficacy and safety of chloral hydrate sedation in infants for pulmonary function tests. *Rev Paul Pediatr*. 2016;34(4):408–411. doi:10.1016/j.rppede.2016.06.001
31. Grissinger M. Chloral hydrate: is it still being used? Are there safer alternatives? *P T*. 2019;44(8):444–459.
32. Litman RS, Soin K, Salam A. Chloral hydrate sedation in term and preterm infants: an analysis of efficacy and complications. *Anesth Analg*. 2010;110(3):739–746. doi:10.1213/ANE.0b013e3181ca12a8
33. Zhang Q, Li H, Dong X, Tu W. Short-term effects of single-dose chloral hydrate on neonatal auditory perception: an auditory event-related potential study. *PLoS One*. 2019;14(2):e0212195. doi:10.1371/journal.pone.0212195
34. Guerra GG, Robertson CMT, Alton GY, et al. Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up. *Pediatr Anesthesia*. 2014;24(3):257–265.
35. Yang X, Gong R, Qin L, et al. Trafficking of NMDA receptors is essential for hippocampal synaptic plasticity and memory consolidation. *Cell Rep*. 2022;40(7):111217. doi:10.1016/j.celrep.2022.111217
36. Yang W, Yu W, Li X, Li X, Yu S. Alpha-synuclein differentially reduces surface expression of N-methyl-d-aspartate receptors in the aging human brain. *Neurobiol Aging*. 2020;90:24–32. doi:10.1016/j.neurobiolaging.2020.02.015
37. Ho YS, Ma HY, Chang HY, et al. Lipid peroxidation and cell death mechanisms in rats and human cells induced by chloral hydrate. *Food Chem Toxicol*. 2003;41(5):621–629.

38. Salort G, Álvaro-Bartolomé M, García-Sevilla JA. Pentobarbital and other anesthetic agents induce opposite regulations of MAP kinases p-MEK and p-ERK, and upregulate p-FADD/FADD neuroplastic index in brain during hypnotic states in mice. *Neurochem Int*. 2019;122:59–72. doi:10.1016/j.neuint.2018.11.008
39. Liu JH, Feng D, Zhang YF, et al. Chloral hydrate preconditioning protects against ischemic stroke via upregulating annexin A1. *CNS Neurosci Ther*. 2015;21(9):718–726. doi:10.1111/cns.12435
40. Al-Gailani L, Al-Kaleel A, Arslan G, Ayyıldız M, Ağar E. THE effect of general anesthetics on genetic absence epilepsy in WAG/Rij rats. *Neurol Res*. 2022;44(11):995–1005. doi:10.1080/01616412.2022.2095706
41. Zhao J, Yan S, Ma X, Song Y, Pan Y. Nrf2 regulates the activation of THP-1 cells induced by chloral hydrate. *Ecotoxicol Environ Saf*. 2023;256:114841. doi:10.1016/j.ecoenv.2023.114841
42. Hamer G, Roepers-Gajadien HL, van Duyn-Goedhart A, et al. DNA double-strand breaks and gamma-H2AX signaling in the testis. *Biol Reprod*. 2003;68(2):628–634. doi:10.1095/biolreprod.102.008672
43. Cardinale A, Saladini S, Lupacchini L, et al. DNA repair protein DNA-PK protects PC12 cells from oxidative stress-induced apoptosis involving AKT phosphorylation. *Mol Biol Rep*. 2022;49(2):1089–1101. doi:10.1007/s11033-021-06934-5
44. Lee M, Suk K, Kang Y, McGeer E, McGeer PL. Neurotoxic factors released by stimulated human monocytes and THP-1 cells. *Brain Res*. 2011;1400:99–111. doi:10.1016/j.brainres.2011.05.021
45. Messmer K, Reynolds GP. An in vitro model of inflammatory neurodegeneration and its neuroprotection. *Neurosci Lett*. 2005;388(1):39–44. doi:10.1016/j.neulet.2005.06.047
46. Chung EN, Lee J, Polonio CM, et al. Psychedelic control of neuroimmune interactions governing fear. *Nature*. 2025;641(8065):1276–1286. doi:10.1038/s41586-025-08880-9
47. Krasowski MD, Harrison NL. The actions of ether, alcohol and alkane general anaesthetics on GABAA and glycine receptors and the effects of TM2 and TM3 mutations. *Br J Pharmacol*. 2000;129(4):731–743. doi:10.1038/sj.bjp.0703087
48. Day M, Belal M, Surmeier WC, et al. GABAergic regulation of striatal spiny projection neurons depends upon their activity state. *PLoS Biol*. 2024;22(1):e3002483. doi:10.1371/journal.pbio.3002483
49. Koh W, Kwak H, Cheong E, Lee CJ. GABA tone regulation and its cognitive functions in the brain. *Nat Rev Neurosci*. 2023;24(9):523–539. doi:10.1038/s41583-023-00724-7
50. Kim G, Kim H, Jang IS. Trichloroethanol, an active metabolite of chloral hydrate, modulates tetrodotoxin-resistant na+ channels in rat nociceptive neurons. *BMC Anesthesiol*. 2023;23(1):145. doi:10.1186/s12871-023-02105-0
51. Barmashenko G, Hefft S, Aertsen A, Kirschstein T, Köhling R. Positive shifts of the GABAA receptor reversal potential due to altered chloride homeostasis is widespread after status epilepticus. *Epilepsia*. 2011;52(9):1570–1578. doi:10.1111/j.1528-1167.2011.03247.x
52. Ge S, Goh ELK, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature*. 2006;439(7076):589–593. doi:10.1038/nature04404
53. Peerboom C, Wierenga CJ. The postnatal GABA shift: a developmental perspective. *Neurosci Biobehav Rev*. 2021;124:179–192. doi:10.1016/j.neubiorev.2021.01.024
54. Ghit A, Assal D, Al-Shami AS, Hussein DEE. GABAA receptors: structure, function, pharmacology, and related disorders. *J Genet Eng Biotechnol*. 2021;19(1):123. doi:10.1186/s43141-021-00224-0
55. Leibovitz Z, Lerman-Sagie T, Haddad L. Fetal brain development: regulating processes and related malformations. *Life*. 2022;12(6):809. doi:10.3390/life12060809
56. Jiang C, Xu Y, Zhong J, et al. Chloral hydrate alters brain activation induced by methamphetamine-associated cue and prevents relapse. *Front Mol Neurosci*. 2022;15:934167. doi:10.3389/fnmol.2022.934167
57. Belrose JC, Noppens RR. Anesthesiology and cognitive impairment: a narrative review of current clinical literature. *BMC Anesthesiol*. 2019;19(1):241. doi:10.1186/s12871-019-0903-7
58. Liu H, Su B, Zhang Z, et al. Neonatal sevoflurane exposures inhibits DHHC5-mediated palmitoylation of TfR1 in oligodendrocytes, leading to hypomyelination and neurological impairments. *J Adv Res*. 2025;2025:S2090123225001079. doi:10.1016/j.jare.2025.02.009
59. Kostović I, Sedmak G, Judaš M. Neural histology and neurogenesis of the human fetal and infant brain. *Neuroimage*. 2019;188:743–773. doi:10.1016/j.neuroimage.2018.12.043
60. Andropoulos DB. Effect of anesthesia on the developing brain: infant and fetus. *Fetal Diagn Ther*. 2018;43(1):1–11. doi:10.1159/000475928
61. Hudson AE, Hemmings HC. Are anaesthetics toxic to the brain? *Br J Anaesth*. 2011;107(1):30–37. doi:10.1093/bja/aer122
62. Wu C, Sun D. GABA receptors in brain development, function, and injury. *Metab Brain Dis*. 2015;30(2):367–379. doi:10.1007/s11011-014-9560-1
63. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci*. 2016;17(11):705–717. doi:10.1038/nrn.2016.128
64. Huang ZJ. Activity-dependent development of inhibitory synapses and innervation pattern: role of GABA signalling and beyond. *J Physiol*. 2009;587(Pt 9):1881–1888. doi:10.1113/jphysiol.2008.168211
65. Tang X, Jaenisch R, Sur M. The role of GABAergic signalling in neurodevelopmental disorders. *Nat Rev Neurosci*. 2021;22(5):290–307. doi:10.1038/s41583-021-00443-x
66. Di J, Li J, O'Hara B, et al. The role of GABAergic neural circuits in the pathogenesis of autism spectrum disorder. *Int J Dev Neurosci*. 2020;80(2):73–85. doi:10.1002/jdn.10005
67. Cellot G, Cherubini E. Functional role of ambient GABA in refining neuronal circuits early in postnatal development. *Front Neural Circuits*. 2013;7:136. doi:10.3389/fncir.2013.00136
68. Ben-Ari Y. The GABA excitatory/inhibitory developmental sequence: a personal journey. *Neuroscience*. 2014;279:187–219. doi:10.1016/j.neuroscience.2014.08.001
69. Li Y. Modern epigenetics methods in biological research. *Methods*. 2021;187:104–113. doi:10.1016/j.ymeth.2020.06.022
70. Adam MA, Harwell CC. Epigenetic regulation of cortical neurogenesis; orchestrating fate switches at the right time and place. *Curr Opin Neurobiol*. 2020;63:146–153. doi:10.1016/j.conb.2020.03.012
71. Covic M, Karaca E, Lie DC. Epigenetic regulation of neurogenesis in the adult hippocampus. *Heredity*. 2010;105(1):122–134. doi:10.1038/hdy.2010.27

72. Jeong H, Mendizabal I, Berto S, et al. Evolution of DNA methylation in the human brain. *Nat Commun*. 2021;12(1):2021. doi:10.1038/s41467-021-21917-7
73. Feng J, Fouse S, Fan G. Epigenetic regulation of neural gene expression and neuronal function. *Pediatr Res*. 2007;61(5 Part 2):58R–63R. doi:10.1203/pdr.0b013e3180457635
74. McKay JA, Adriaens ME, Ford D, Relton CL, Evelo CTA, Mathers JC. Bioinformatic interrogation of expression array data to identify nutritionally regulated genes potentially modulated by DNA methylation. *Genes Nutr*. 2008;3(3–4):167–171. doi:10.1007/s12263-008-0095-0
75. Horrillo A, Pezzolla D, Fraga MF, et al. Zebularine regulates early stages of mESC differentiation: effect on cardiac commitment. *Cell Death Dis*. 2013;4(4):e570. doi:10.1038/cddis.2013.88
76. Montgomery T, Uh K, Lee K. TET enzyme driven epigenetic reprogramming in early embryos and its implication on long-term health. *Front Cell Dev Biol*. 2024;12:1358649. doi:10.3389/fcell.2024.1358649
77. Schulz M, Teissandier A, De La Mata Santaella E, et al. DNA methylation restricts coordinated germline and neural fates in embryonic stem cell differentiation. *Nat Struct Mol Biol*. 2024;31(1):102–114. doi:10.1038/s41594-023-01162-w
78. Zheleznyakova GY, Cao H, Schiöth HB. BDNF DNA methylation changes as a biomarker of psychiatric disorders: literature review and open access database analysis. *Behav Brain Funct*. 2016;12(1):17.
79. Kundakovic M, Gudsnuk K, Herbstman JB, Tang D, Perera FP, Champagne FA. DNA methylation of BDNF as a biomarker of early-life adversity. *Proc Natl Acad Sci USA*. 2015;112(22):6807–6813. doi:10.1073/pnas.1408355111
80. Ikegame T, Bundo M, Murata Y, Kasai K, Kato T, Iwamoto K. DNA methylation of the BDNF gene and its relevance to psychiatric disorders. *J Hum Genet*. 2013;58(7):434–438. doi:10.1038/jhg.2013.65
81. Ghersi-Egea JF, Saudrais E, Strazielle N. Barriers to drug distribution into the perinatal and postnatal brain. *Pharm Res*. 2018;35(4):84. doi:10.1007/s11095-018-2375-8
82. Kobayashi T, Takeba Y, Ohta Y, et al. Prenatal glucocorticoid administration enhances bilirubin metabolic capacity and increases Ugt1a and Abcc2 gene expression via glucocorticoid receptor and PXR in rat fetal liver. *J Obstet Gynaecol Res*. 2022;48(7):1591–1606. doi:10.1111/jog.15235
83. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther*. 2014;19(4):262–276. doi:10.5863/1551-6776-19.4.262
84. George MH, Moore T, Kilburn S, Olson GR, DeAngelo AB. Carcinogenicity of chloral hydrate administered in drinking water to the male F344/N rat and male B6C3F1 mouse. *Toxicol Pathol*. 2000;28(4):610–618. doi:10.1177/019262330002800415
85. Dexmedetomidine-induced stimulation of glutamine oxidation in astrocytes: a possible mechanism for its neuroprotective activity - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/10894172/. Accessed June 18, 2025.
86. Lin Y, Zhang R, Shen W, et al. Dexmedetomidine versus other sedatives for non-painful pediatric examinations: a systematic review and meta-analysis of randomized controlled trials. *J Clin Anesth*. 2020;62:109736. doi:10.1016/j.jclinane.2020.109736
87. Cui Y, Gong T, Mu Q, et al. Predictors of pediatric sedation failure with initial dose of intranasal dexmedetomidine and oral midazolam. *Pediatr Res*. 2023;94(6):2054–2061. doi:10.1038/s41390-023-02758-0
88. Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. *CNS Drugs*. 2015;29(7):543–563. doi:10.1007/s40263-015-0259-6
89. Ebrahimi M, Dabbagh A, Madadi F. Propofol-induced hippocampal neurotoxicity: a mitochondrial perspective. *Brain Res*. 2024;1831:148841. doi:10.1016/j.brainres.2024.148841
90. Peter JU, Dieudonné P, Zolk O. Pharmacokinetics, Pharmacodynamics, and Side Effects of Midazolam: a Review and Case Example. *Pharmaceuticals*. 2024;17(4):473. doi:10.3390/ph17040473
91. Walters RJ, Hadley SH, Morris KD, Amin J. Benzodiazepines act on GABAA receptors via two distinct and separable mechanisms. *Nat Neurosci*. 2000;3(12):1274–1281. doi:10.1038/81800
92. Azemati S, Keihani M, Sahmeddini MA, et al. Comparing the sedative effects of intranasal dexmedetomidine midazolam and ketamine in outpatient pediatric surgeries: a randomized clinical trial. *Iran J Med Sci*. 2024;49(7):421. doi:10.30476/ijms.2023.99122.3118
93. Jung SM. Drug selection for sedation and general anesthesia in children undergoing ambulatory magnetic resonance imaging. *Yeungnam Univ J Med*. 2020;37(3):159–168. doi:10.12701/yujm.2020.00171
94. Sun M, Xie Z, Zhang J, Leng Y. Mechanistic insight into sevoflurane-associated developmental neurotoxicity. *Cell Biol Toxicol*. 2022;38(6):927–943. doi:10.1007/s10565-021-09677-y
95. Cheng X, Chen Z, Zhang L, et al. Efficacy and safety of midazolam oral solution for sedative hypnosis and anti-anxiety in children: a systematic review and meta-analysis. *Front Pharmacol*. 2020;11:225. doi:10.3389/fphar.2020.00225
96. Lyu X, Tao Y, Dang X. Efficacy and safety of intranasal dexmedetomidine vs. oral chloral hydrate for sedation in children undergoing computed tomography/magnetic resonance imaging: a meta-analysis. *Front Pediatr*. 2022;10:872900. doi:10.3389/fped.2022.872900
97. Khan A, Sinha R, Kumar KR, Velpandian T, Maitra S, Ray BR. Comparison of plasma concentration and sedative effect of sublingual and intranasal dexmedetomidine in children: a double-blind randomised controlled study. *Acta Anaesthesiol Scand*. 2025;69(3):e14583. doi:10.1111/aas.14583
98. Ferrazzano GF, Cantile T, Quaraniello M, et al. Effectiveness and safety of intravenous sedation with propofol in non-operating room anesthesia (NORA) for dental treatment in uncooperative paediatric patients. *Children*. 2021;8(8):648. doi:10.3390/children8080648
99. Hannallah RS, Baker SB, Casey W, McGill WA, Broadman LM, Norden JM. Propofol: effective dose and induction characteristics in unpremedicated children. *Anesthesiology*. 1991;74(2):217–219.
100. Ageel M. Review of pediatric sedation and anesthesia for radiological diagnostic and therapeutic procedures. *J Radiat Res Appl Sci*. 2024;17(1):100833. doi:10.1016/j.jrras.2024.100833
101. Bhatt M, Johnson DW, Chan J, et al. Risk factors for adverse events in emergency department procedural sedation for children. *JAMA Pediatr*. 2017;171(10):957. doi:10.1001/jamapediatrics.2017.2135
102. Green SM, Roback MG, Krauss B, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med*. 2009;54(2):158–168.e4. doi:10.1016/j.annemergmed.2008.12.011

103. Poonai N, Canton K, Ali S, et al. Intranasal ketamine for procedural sedation and analgesia in children: a systematic review. *PLoS One*. 2017;12(3):e0173253. doi:10.1371/journal.pone.0173253
104. Nishijima M, Yoshida T, Matsumura K, et al. Correlation between the bayley-III at 3 years and the wechsler intelligence scale for children, fourth edition, at 6 years. *Pediatr Int*. 2022;64(1):e14872. doi:10.1111/ped.14872
105. Lace JW, Merz ZC, Kennedy EE, et al. Examination of five- and four-subtest short form IQ estimations for the wechsler intelligence scale for children-fifth edition (WISC-V) in a mixed clinical sample. *Appl Neuropsychol Child*. 2022;11(1):50–61. doi:10.1080/21622965.2020.1747021
106. Srivastav AK, Mishra MK, Lillard JW, Singh R. Transforming pharmacogenomics and CRISPR gene editing with the power of artificial intelligence for precision medicine. *Pharmaceutics*. 2025;17(5):555. doi:10.3390/pharmaceutics17050555
107. Herrera-Zamora JM, Castro-Sánchez LA, Reyes-Mendez M, et al. Development-dependent changes in the NR2 subtype of the N-methyl-D-aspartate receptor in the suprachiasmatic nucleus of the rat. *J Biol Rhythms*. 2019;34(1):39–50. doi:10.1177/0748730418824198
108. Chugani DC, Muzik O, Juhász C, Janisse JJ, Ager J, Chugani HT. Postnatal maturation of human $GABA_A$ receptors measured with positron emission tomography. *Ann Neurol*. 2001;49(5):618–626. doi:10.1002/ana.1003

Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/drug-design-development-and-therapy-journal