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PERSPECTIVES

A hospital-based cost minimization study of the potential financial impact on the UK health care system of introduction of iron isomaltoside 1000

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Background: The clinical need to be able to administer high doses of intravenous iron conveniently in a single rapid infusion has been addressed by the recent introduction of ferric carboxymaltose and subsequently iron isomaltoside 1000. Neither requires a test dose. Ferric carboxymaltose can be administered at 15 mg/kg body weight to a maximum dose of 1000 mg, whereas iron isomaltoside 1000 can be administered at 20 mg/kg body weight. The ability to give high doses of iron is important in the context of managing iron deficiency anemia in a number of clinical conditions where demands for iron are high (including chronic blood loss associated with inflammatory bowel disease, menorrhagia, and chronic kidney disease). It is also an important component in the strategy as an alternative to a blood transfusion. Affordability is a key issue for health services.

Methods: This study was a comparative analysis of the costs of administering the newly available intravenous iron formulations against standard practice (blood transfusion, intravenous iron sucrose) by considering the cost of this treatment option plus nursing costs associated with administration, equipment for administration, and patient transportation in the secondary care (hospital) setting across three dosage levels (600 mg, 1000 mg, and 1600 mg).

Results and conclusion: The analysis indicates that the use of iron isomaltoside 1000 results in a net saving when compared with iron sucrose, blood, and ferric carboxymaltose. At 600 mg and 1000 mg doses, it is cheaper than low-molecular-weight iron dextran but more expensive at a dose of 1600 mg. However, it takes six hours to administer low-molecular-weight iron dextran at this dose level, which is inconvenient and reduces patient throughput (productivity).

Keywords: iron isomaltoside 1000, iron deficiency anemia, high dose, single dose, parenteral iron, cost minimization

Introduction

Blood is a declining resource. The safety associated with the receipt of a blood infusion has progressively improved over the last decade but there are recognized risks associated with a blood transfusion.[1] Strategies to reduce the risk have led to the imposition of restrictions on members of the population that can be donors. This has resulted in a decline in the volume of blood donated. Additionally, following the identification of blood-borne diseases in blood donated by UK donors (eg, prion-related diseases, including Creutzfeldt-Jakob disease), certain cohorts of the population are prevented from receiving blood and blood products prepared from blood donated in the UK.

The National Blood Transfusion Service has encouraged the conservation and appropriate use of blood and blood products.[2] In addition, reducing inappropriate blood use policy is aimed at reducing the risk associated with the process of matching

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and administering blood in the secondary and tertiary care settings.

These developments have been at a time when the importance, implications, and prevalence of iron deficiency anemia is being appreciated and associated with a broad range of clinical conditions and situations:

- In chronic kidney disease patients with/without erythropoietin replacement therapy
- In patients undergoing various modes of dialysis therapy
- Anemia associated with pregnancy (pre/postpartum, following hemorrhage)
- Anemia following "blood-thirsty" surgical procedures eliminating or reducing the need for postsurgery transfusion (eg, orthopedics, colorectal surgery)
- In surgery associated with the elderly (who are often iron-deficient and/or anemic)
- Iron deficiency anemia associated with anemia of chronic disease
- Chronic iron deficiency anemia (often presenting with acute symptoms)
- Chronic occult blood loss (inflammatory bowel disease)
- Anemia associated with cancer or the use of chemotherapeutic agents
- Menorrhagia (heavy uterine bleeding).

Iron increasingly plays a major role in "blood conservation" policies. Thus, in the situations outlined above, iron store repletion can result in erythropoiesis, ie, restoring or improving hemoglobin levels. This can commonly be achieved without the need for concomitant erythropoiesis-stimulating therapy.[3]

Anemia of chronic disease may be a comorbidity of a number of chronic conditions. In these conditions, where hepcidin blocks both the absorption of iron from the gastrointestinal tract and release of stored iron, intravenous iron has been demonstrated as being able to bypass these blocks and act as the substrate for erythropoiesis.[4,5] Compared with oral iron, intravenous iron repletes iron stores more rapidly, and can be given at high doses as a total dose infusion which improves compliance. Oral iron is associated with poor tolerance, poor compliance, a high frequency of adverse events, and less rapid restoration of iron stores. It is poorly absorbed in patients with anemia of chronic disease. As such, its role as a useful source of iron supplementation is limited.

The administration of intravenous iron may be considered a more physiological method of addressing chronic iron deficiency anemia than a blood transfusion. A transfusion addresses the acute symptoms of anemia, but is a poor and expensive source of iron, whereas intravenous iron provides physiologically available iron for both erythropoiesis and replenishing iron stores.

The purpose of this paper was to examine the comparative cost to the health care economy of the intravenous iron supplementation options, including blood transfusions. The economic importance is driven by the need to optimize the use of services in the current challenging financial climate in parallel with serving the needs of patients. In these circumstances, value for money and the overall relative cost of treatments are important when making policy prescribing decisions. Given that all options will achieve similar clinical responses, a cost minimization analysis was undertaken to determine the least expensive option overall.

Background

Iron is an essential metabolic element. The human body requires about 3 g of elemental iron daily. Iron cannot be actively excreted. Iron loss is passive. In a healthy individual it occurs through the sloughing off of the intestinal enterocytes (gut lining). In ill health, blood loss may contribute to iron loss (as may the taking of frequent blood samples for hematinic studies). The main physiological control mechanism is somewhat complex (Figure 1).

Iron absorption is affected by a number of parameters, including iron depletion and is restricted by inflammation. The precise mechanism is not fully elucidated, but involves the protein, hepcidin, a 25-amino acid synthesized in the liver. Hepcidin acts as a regulator of iron metabolism which has important effects on iron absorption, transportation, and storage.[6] Hepcidin binds to the iron exporter protein, ferroportin, which causes internalization and degradation of iron.[7] This interaction leads to reduced red cell iron absorption and sequestration in the reticuloendothelial system. Stimuli such as hypoxia, as a result of anemia, may also inhibit hepcidin, via hypoxia-inducible factor, leading to increased iron absorption.

Although iron is essential to life it is also potentially toxic. This has affected the ability to prepare safe formulations for intravenous administration. Early intravenous formulations were associated with adverse effects, which were occasionally severe. With the recent controversies involving erythropoiesis-stimulating therapy, there has been a renewed desire to develop intravenous iron formulations that can be administered at flexible dosage levels, and given at a rate compatible with both patient convenience and compliance, and in a timely manner for health care professionals.[8–10]

The introduction of a high-molecular-weight iron dextran formulation (no longer available in Europe) was a first step in

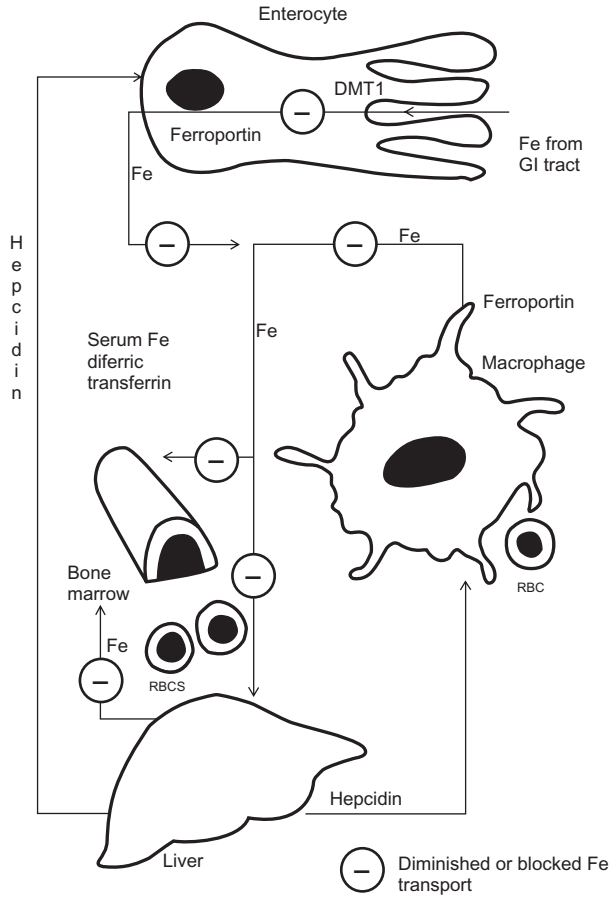

Figure 1 Schematic diagram of the role of hepcidin affecting the movement of iron.*
Note: *Developed from Gantz et al[7] and Gantz et al.[6]
Abbreviations: DMT I, divalent metal transporter I; GI, gastrointestinal; RBCS, red blood cells; Fe, iron.

iron repletion. This was administered slowly over a number of hours and was associated with a high frequency of adverse events. Iron sucrose and subsequently low-molecular-weight iron dextran were introduced in the late 1990s.

Low-molecular-weight iron dextran offers a flexible dose regimen, and can be delivered as a 100 mg intramuscular injection, as a slow intravenous injection (up to 200 mg iron), as an intravenous drip infusion (up to 200 mg), or as a total dose infusion (Tables 1, 2 and 3). A total dose infusion allows high doses (20 mg/kg) to be administered in a single infusion, but over a period of time - normally six hours. A test dose is required prior to administration.[11]

Iron sucrose can be administered in a single bolus injection limited to 100 mg, given as a slow injection over five minutes or 200 mg over 10 minutes (Table 2). If given by infusion, 100 mg is given over 15 minutes and 200 mg over 30 minutes (maximum three per week, maximum dose 600 mg/week) (Table 1).[12]

In the UK for the past decade, these products have provided the means to administer iron via the parenteral route, albeit with limitations. In 2008, ferric carboxymaltose was introduced to the UK. This formulation contains iron in its ferric state as a complex with a carbohydrate polymer, does not require a test dose, and can be administered as an infusion at a dose of 15 mg/kg body weight to a maximum of 1000 mg in a single infusion if the patient weighs at least 67 kg (Table 1, 2 and 3).[13] More recently, iron isomaltoside 1000 has been approved for marketing in Europe. A test dose is not required and doses can be administered up to 20 mg/kg to the full body weight.[14] Individuals with a minimum body weight of 50 kg can receive a 1000 mg dose (Tables 1, 2 and 3). This allows more patients to achieve iron repletion in a single rapid infusion. This is a nondextran, low anaphylactic, nonbranched carbohydrate chain with a molecular weight below 1000 Da.[14]

Methods

The purpose of this study was to examine the cost of administering iron isomaltoside 1000 and ferric carboxymaltose, and to compare these with existing standard treatments. The cost of administering iron isomaltoside 1000 and ferric carboxymaltose was compared with the cost of administering a blood transfusion, iron sucrose, and low-molecular-weight iron dextran across a range of doses in a secondary care (hospital) setting. The costs included transport (to reflect

Table 1 Comparative intravenous drip infusion regimens[11–14,29]

Product →	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood
Dose limitation	100 mg or 200 mg	100 mg or 200 mg	20 mg/kg body weight to total body weight	15 mg/kg up to max 1000 mg	None
Rate of administration	100 mg in 37.5 mins 200 mg in 67.5 mins	100 mg in 37.5 mins 200 mg in 41.25 mins	0–5 mg/kg body weight in 15 mins 6–10 mg/kg body weight in 30 mins 11–20 mg/kg body weight in 60 mins	100 mg–200 mg no minimum time quoted 200 mg–500 mg 6 mins	1 unit (equ. 200 mg iron) 90 mins
Test dose	Required for first administration	Required at each administration	Not required	Not required	N/A

Table 2 Comparative intravenous bolus injection regimens[11–14]

Product →	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood
Dose limitation	100 mg or 200 mg	100 mg or 200 mg	100–200 mg	Up to 200 mg	N/A
Rate of administration	100 mg in 20 mins 200 mg in 25 mins	100 mg in 25 mins 200 mg in 35 mins	2–4 mins	By injection (push)	N/A
Test dose	Required for first administration	Required at each administration	Not required	Not required	N/A

patient status, ie, ambulatory or nonambulatory) and nursing costs (salary band 6 and 7). This was undertaken to provide a degree of robustness for the estimations. Analysis in the community was beyond the scope of this analysis because cost data were lacking to perform a comparative analysis (eg, rent).

Parameters for the cost model

Standard treatment comparators

Standard treatment will vary according to local practice and indication. Traditionally, prior to the introduction of intravenous iron, blood (units of packed red blood cells) would have been the sole option in most of the indications/situations described earlier. Iron supplementation is increasingly used as an alternative. Intravenous iron is now used almost exclusively in hemodialysis patients, whereas in other situations, intravenous iron is progressively replacing the practice of administering a blood transfusion.

Given the European legislation in pursuit of reducing the risk associated with blood use and the appropriate use of blood, and in recognition that intravenous iron can provide a viable alternative, blood is included as a comparator.[15,16] Iron sucrose and low-molecular-weight iron dextran are also used as comparators.

Dose levels

The comparator doses have been chosen to reflect clinical practice. Blood is transfused in multiples of "units". Each unit may be considered to approximate to 200 mg of iron.

Iron doses are commonly estimated using the Ganzoni formula that reflects body weight, the difference between actual hemoglobin level and target hemoglobin level, and the desired level of iron stores (commonly 500 mg).[17] It is not uncommon for an individual's requirement to be up to 2000 mg across the range of conditions associated with anemia.[18–22] Limitations of the previously available intravenous iron supplements include the number and frequency of doses needed to achieve high level repletion when using iron sucrose and duration of administration for low-molecular-weight iron dextran.

For the purposes of the cost minimization modeling three levels of administration have been chosen (to provide a dose sensitivity matrix), ie, 600 mg, 1000 mg, and 1600 mg. These allow direct comparison with units of blood (multiples of units each equivalent to 200 mg of elemental iron). The profiles of the two products, which have recently entered the market, allow high-dose use. The various doses have been constructed in a matrix that reflects cost assumptions appropriate for the range of doses.

Bioavailability and efficacy

In preparing this model, it was assumed that each of the intravenous iron preparations impact erythropoiesis and enter iron stores in a similar manner directly related to the dose administered. Whilst during the acute administration phase there may be differences in pharmacokinetic properties (such as differences in binding to the glucose moiety and rates of release of free iron) leading to potential

Table 3 Comparative high-dose infusion regimens[11–14]

Product →	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood
Dose limitation	200 mg/administration	20 mg/kg	20 mg/kg	15 mg/kg max 1000 mg	N/A
Rate of administration	N/A*	20 mg/kg first 25 mg (test dose) over 15 mins then balance to 45–60 drops/min	0–10 mg/kg in 30 mins 11–20 mg/kg in 60 mins	<500 mg in 6 mins 500–1000 mg in 15 mins	N/A
Test dose	N/A	Required at each administration	Not required	Not required	N/A

Note: *NB requires multiple administrations of 200 mg intravenous injections to deliver total dose.
Abbreviation: N/A, not applicable.

activation of oxidative stress processes, there is no evidence to suggest that incorporation of iron into reticulocytes, elevation of hemoglobin levels, and development of iron stores will differ.[23–27]

The administration of intravenous iron differs physiologically to the administration of a blood transfusion. Blood results in an immediate rise in hemoglobin level. This will decline as the erythrocytes die (average life 120 days in patients with normal renal function). Iron from a blood transfusion is then recycled as the erythrocytes expire. Blood has traditionally been used to treat iron deficiency anemia and may still be regarded as "standard treatment".

Adverse events

In the cost modeling, no allowance is made for occurrence of adverse events. These are infrequent and similar for iron sucrose and low-molecular-weight iron dextran.[11,12,28] The summaries of product characteristics for iron isomaltoside 1000 and ferric carboxymaltose indicate that adverse events associated with their use will be similar to those of currently available intravenous iron formulations.[11–14]

Blood has higher levels of risk, both as a product per se and from the potential human error associated with compatibility testing and administration. Intravenous iron can be used universally (irrespective of blood type), has very limited contraindications, has a good shelf-life, and does not need controlled refrigerated storage conditions.

Dose and rate of administration limitations

In the cost modeling, sensitivity to the dose and rate of administration of the various products were considered. The following information (as per the relevant manufacturers' summary of product characteristics), eg, rate of delivery and maximum dose, was included.

The manufacturers' instructions for undertaking a test dose reflect whether the patient is receiving the medication for the first or subsequent time. For low-molecular-weight iron dextran, if administering for the first time, a 25-mg dose is administered and the patient observed for 45 minutes.[11] The balance can be administered if there are no adverse events. For the second and subsequent infusions, the first 25 mg of iron is infused over 15 minutes and, if there are no untoward events, the administration can be continued.[11] When a total dose is administered, the patient should be observed for a further hour after the completion of the administration.[11] For the administration of iron sucrose, a test dose is required only for the first administration to a patient.[12]

For the purposes of this study, it was assumed that this was the second (or subsequent) administration to a patient of iron sucrose and low-molecular-weight iron dextran. For the specified range of doses, an observation period was included in the administration times for low-molecular-weight iron dextran (as indicated in the manufacturer's summary of product characteristics).[11] Given the recommended dilution volume for preparing the infusion, it was assumed that the administration plus observation period would be similar at each dose level, ie, six hours in total. In this analysis, 10 minutes was allowed for infusion setup time across the range of preparations.

Transportation

This is an important factor when considering intravenous iron supplementation. Historically patients with chronic kidney disease (and chronic anemia) requiring dialysis would arrive at hospital on a stretcher or in a wheelchair. The availability of intravenous iron and erythropoiesis-stimulating agents directly affects energy and ambulatory capability in many individuals. Across the spectrum of patients with iron deficiency anemia, a proportion will be short of breath, perhaps with palpitations, will invariably be nonambulatory, and will be transported to hospital on a stretcher or in a wheelchair.

In the UK, ambulance services are paid by the NHS (the public health service economy). For the purposes of this study, two types of "transported" patient are considered, ie, those who are ambulatory, where the charge is £12.00/single journey (£24.00 return) and those who are in a wheelchair or who require a stretcher where the charge for a single journey is £48.00 single (£96.00 return).[30]

Across the spectrum of causes of iron deficiency anemia, it is difficult to establish specifically the proportion of patients that require transportation and the ratio between ambulatory and nonambulatory for those who are anemic. It is realized that a proportion of patients will use self transport (or that of a friend or relative). For the purposes of this study, we have used a sensitivity matrix at two levels for the patient population that require transport, ie, 10% and 20%. It is assumed that those requiring transport will be equally split between those who are ambulatory and those who are nonambulatory and who require a stretcher or wheelchair. The costs used were £24.00 per return journey for ambulatory patients and £96.00 per return journey for nonambulatory patients.

The transport costs were taken from a report from the Doncaster and Bassetlaw Hospitals NHS Foundation Trust which indicated £48.00/journey (stretcher/wheelchair) and

Table 4 Comparative treatment costs and incremental expenditure over the cost of iron isomaltoside 1000 for the administration of 600 mg of iron in nonhemodialysis patients

	Comparative costs (£)					Cost savings (£) Cost difference ± % compared to iron isomaltoside 1000			
	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood	Iron isomaltoside 1000 vs iron sucrose	Iron isomaltoside 1000 vs low-molecular-weight iron dextran	Iron isomaltoside 1000 vs ferric carboxymaltose	Iron isomaltoside 1000 vs blood
10% patients transported									
Nurse band 6	230.51	200.71	161.54	179.59	465.39	68.97 (+42.7%)	39.17 (+24.2%)	18.05 (+11.2%)	303.85 (+188.1%)
Nurse band 7	250.51	221.27	168.20	183.75	473.45	82.31 (+48.9%)	53.07 (+31.6%)	15.55 (+9.2%)	305.25 (+181.5%)
20% patients transported									
Nurse band 6	248.51	206.71	167.54	191.59	471.95	80.97 (+48.3%)	39.17 (+23.4%)	24.05 (+14.4%)	304.41 (+181.7%)
Nurse band 7	268.51	227.27	174.20	195.75	479.45	94.31 (+54.1%)	53.07 (+30.5%)	21.55 (+12.4%)	305.25 (+175.2%)

Table 5 Comparative treatment costs and incremental expenditure over the cost of iron isomaltoside 1000 for the administration of 1000 mg of iron in nonhemodialysis patients

	Comparative costs (£)					Cost savings (£) Cost difference ± % compared to iron isomaltoside 1000			
	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood	Iron isomaltoside 1000 vs iron sucrose	Iron isomaltoside 1000 vs low-molecular-weight iron dextran	Iron isomaltoside 1000 vs ferric carboxymaltose	Iron isomaltoside 1000 vs blood
10% patients transported									
Nurse band 6	384.18	232.59	223.75	266.59	766.47	160.43 (+71.7%)	8.84 (+4.0%)	42.84 (+19.1%)	542.72 (+242.6%)
Nurse band 7	417.52	253.15	229.59	270.75	778.97	187.93 (+81.9%)	23.56 (+10.3%)	41.16 (+17.9%)	549.38 (+239.3%)
20% patients transported									
Nurse band 6	414.18	238.59	229.75	278.59	772.47	184.43 (+80.3%)	8.84 (+3.8%)	48.84 (+21.3%)	542.72 (+236.2%)
Nurse band 7	447.52	259.15	235.59	282.75	784.97	211.93 (+90.0%)	23.56 (+10.0%)	47.16 (+20.0%)	549.38 (+233.2%)

Table 6 Comparative treatment costs and incremental expenditure over the cost of iron isomaltoside 1000 for the administration of 1600 mg of iron in nonhemodialysis patients

	Comparative costs (£)					Cost savings (£) Cost difference ± % compared to iron isomaltoside 1000			
	Iron sucrose	Low-molecular-weight iron dextran	Iron isomaltoside 1000	Ferric carboxymaltose	Blood	Iron isomaltoside 1000 vs iron sucrose	Iron isomaltoside 1000 vs low-molecular-weight iron dextran	Iron isomaltoside 1000 vs ferric carboxymaltose	Iron isomaltoside 1000 vs blood
10% patients transported									
Nurse band 6	614.69	280.41	325.45	434.17	1217.25	289.24 (+89%)	–45.04 (–13.8%)	108.72 (+33.4%)	891.80 (+274.0%)
Nurse band 7	668.03	300.97	331.29	442.51	1237.25	336.74 (+101.6%)	–30.32 (–9.2%)	111.22 (+33.6%)	905.96 (+273.5%)
20% patients transported									
Nurse band 6	662.69	286.41	331.45	446.17	1223.25	331.24 (+99.9%)	–45.04 (–13.6%)	114.72 (+34.6%)	891.80 (+269.1%)
Nurse band 7	716.03	306.97	337.29	454.51	1243.25	378.74 (+112.3%)	–30.32 (–9.0%)	117.22 (+34.8%)	905.96 (+268.6%)

£12.00 for ambulatory patients using an ambulance in 2007.[30] The Personal Social Services Research Unit (Unit Costs of Health, University of Kent) quoted the cost as £54.00 per urban patient journey in 2008.[31] The lower costing has been used in this analysis.

Giving sets, cannula, and dressing

The cost of consumables varies across hospital establishments but, for the purpose of this analysis, unit costs reported by Bhandari and Naudeer[32] were used. These were £7.89 for a "giving set"; £0.74 for one cannula, and £0.54 for a standard dressing.

Nursing time

In the nonrenal setting, it is probable that an anemia nurse will attend to patients either in a specialist clinic or medical diagnostic unit. Nursing costs have been estimated using the hourly costs associated with a band 6 and band 7 nurse, using the midband range increment. The costs were taken from the Personal Social Services Research Unit and are appropriate for a 'nurse led' clinical service.[33] The costs for one hour of 'patient contact' nursing time in the UK at midband 6 and 7 are £67.00 and £77.00, respectively. In the cost allocations, assumptions were made with regard to allocating time to represent multitasking (ie, not dedicating sole time to an individual patient during a six-hour low-molecular-weight iron dextran total dose infusion). Thus, for a short (approximately 30-minute) administration time, a nurse is likely to attend for the duration. For an infusion taking about 60 minutes, it is assumed that the nurse will spend 50% of his/her time with the patient, whereas for a prolonged infusion of low-molecular-weight iron dextran, a nurse is considered to spend 33% of his/her time with the patient (during the test dose phase and observation phase this may be 100%). This sensitivity has been used for both a band 6 and band 7 nurse.

Cost of intravenous iron products

Prices were taken from the British National Formulary or from the manufacturer. For 200 mg iron, these were £17.00 for iron sucrose,[34] £15.94 for low-molecular-weight iron dextran,[34] £43.50 for ferric carboxymaltose,[34] and £33.90 for iron isomaltoside 1000.[35]

Cost of blood

In some countries blood is not charged either to the patient, the providing institution or hospital, or payer. However, there is a cost to the health care economy and, as such, is

appropriate for its costs to be included as a comparator. The costs used in this modeling are those charged in England and Wales to NHS hospitals for 2009/10 and are £133.51/unit for red blood cells, not including the cost of pretransfusion cross-matching of the patient's blood and error checking.[36] This cost is difficult to find or calculate and, in the context of the cost of blood per se, this does not have a major affect on the final analysis. The time for administration of a blood transfusion (one unit) is at least 90 minutes (and up to 180 minutes), except in a situation of major hemorrhage.[29]

Other costs considered minor or unlikely to be significant to the outcomes were excluded. This can be justified on the basis that, in any particular unit, the practice is likely to have a similar impact across the intravenous iron options. A cost deliberately omitted was that of the clinician. Whilst likely to be available during a transfusion, he/she would be undertaking other clinical/administrative duties, whilst a nurse would normally be responsible for administering the infusion and managing/monitoring the procedure. An example of a minor cost is that of the infusion fluid (normal saline) which costs £0.70 per 250 mL.[32]

Results

A matrix was prepared to compare the full cost of administration of the three different dose levels of intravenous iron (as may be required for treating iron deficiency anemia in Stage 5 chronic kidney disease patients or patients with any of the other conditions associated with iron deficiency anemia). From these cost minimization models, at each dose level, the cost of administering iron isomaltoside 1000 is the lowest cost option when compared with what may be considered standard treatments, ie, blood or iron sucrose. Iron isomaltoside 1000 is less expensive than both at doses of 600 mg, 1000 mg, and 1600 mg.

Compared with ferric carboxymaltose, the cost of administering iron parenterally at the three dose levels is again achieved at a comparatively lower cost when using iron isomaltoside 1000 at each dose level and at each level of sensitivity (nurse grade and patient transportation). As the dose of iron administered increases, the actual and percentage saving from using iron isomaltoside 1000 compared with ferric carboxymaltose increases.

Iron isomaltoside 1000 offers cost advantages compared with using blood, iron sucrose, and ferric carboxymaltose in each of the matrices at the three dose levels. When compared with low-molecular-weight iron dextran, iron isomaltoside 1000 is more expensive at the 1600 mg dose level. However, it is cost beneficial at the dose levels of 600 mg and 1000 mg across all sensitivity parameters (Tables 4, 5 and 6).

Discussion

Blood continues to be used to treat iron deficiency anemia, in the absence of acute blood loss, in a number of conditions. NHS Blood and Transplant have established policies to reduce blood use, which includes the use of intravenous iron as an alternative to blood.[2] Intravenous iron is used to treat iron deficiency anemia in many clinical situations and in an increasing number of specialties. In a cost- and time-effective health care environment, it is appropriate to examine the relative costs of administering newly introduced treatments and compare these with existing interventions. This is particularly relevant to the use of intravenous iron as an alternative to a blood transfusion.

Renal medicine has been at the forefront of pioneering the use of intravenous iron, initially in hemodialysis patients, resulting in a dramatic reduction in the requirement for blood transfusions. This practice has largely reflected the availability of iron sucrose. Iron sucrose can be administered in doses up to 200 mg in a single administration and, as such, it was adopted in hemodialysis units and given to patients during one of their weekly hemodialysis sessions.

The use of iron to address iron deficiency anemia associated with chronic kidney disease stages 1–4 has now extended to low clearance (predialysis, Stage 5 nondialysis) patients and patients undergoing continuous ambulatory peritoneal dialysis. These patients attend their renal units only occasionally. To achieve iron adequacy, to replete stores, and meet erythropoietic needs (functional and absolute), large doses of intravenous iron are administered on a low frequency basis (normally every 3–12 months), and hence the need for the ability to administer total repletion doses. This can be achieved by administering multiple doses of 200 mg (iron sucrose) or from a total repletion dose of iron at a single visit. Note that chronic kidney disease patients in the nondialysis (Stage 5) stage of disease progression and those undergoing continuous ambulatory peritoneal dialysis are unlike the hemodialysis patients who attend clinic two or three times each week for dialysis, and who normally receive small doses of iron weekly or every two weeks during a dialysis session.

In a few renal units in the UK, the rate of administration of low-molecular-weight iron dextran has been accelerated with the aim of reducing infusion times and improving productivity (patient throughput).[32,37] This practice is outside of the administration procedure stated in the manufacturer's summary of product characteristics and is not standard

procedure, but illustrates the clinical need and desire to be able to give total doses of intravenous iron more rapidly.

The results of this cost minimization modeling (Tables 4, 5 and 6) indicate that iron isomaltoside 1000 offers cost savings at three dose levels, across a range of sensitivities, when compared with blood and iron sucrose, which are considered to be the current standard of care. Likewise, across the same dose ranges, iron isomaltoside 1000, the most recent introduction, offers savings when compared with ferric carboxymaltose.

The findings with regard to the comparative costs associated with low-molecular-weight iron dextran are less equivocal, in that using the 1600 mg dose model, the outcome slightly favors low-molecular-weight iron dextran (Table 6). At the 1600 mg level, the maximum additional cost if using iron isomaltoside 1000 compared with low-molecular-weight iron dextran would be £45.04 (13.8%). This suggests that low-molecular-weight iron dextran could be considered, based solely on cost, for patients receiving a dose of 1600 mg. However, in the modeling, no account or value is placed on inconvenience to the patient (time in clinic) or the opportunity cost of throughput by occupying a bed or treatment chair for over six hours. Such modeling looks at variable costs and does not allocate overhead costs or consider unit throughput efficiency. This has implications in the payment by results system.

The key cost drivers are cost of medication, time to administer (affecting nurse resource), and transportation. The cost of the various iron formulations are NHS acquisition prices. Nursing costs have been calculated at two grade levels. Additional assumptions relate to time spent with patients during administration. This will be further affected by location of administration (eg, ward, medical investigations unit, hematology day unit). Observation and consultation resulted in allocating 12.5% of a nurse's time to a blood transfusion; 33% of the time was allocated to a patient receiving low-molecular-weight iron dextran and 50% to a patient being administered iron isomaltoside 1000 (at doses of 1000 mg and 1600 mg). At the 600 mg dose level, the administration can be undertaken in 30 minutes for a patient over 60 kg in body weight, so a nurse will spend his or her full time with the patient.

With regard to transportation, the frequency and type needed will reflect a number of factors, including underlying causative condition, age, comorbidities, disabilities, mental capability, social support network, and urban versus rural domicile. To reflect this, transport was assumed to be necessary for 10% and 20% of the population and, at each level, half were ambulatory and half were nonambulatory. The costs used were £12.00/ambulatory patient and £48.00/nonambulatory patient for a single journey. This is considerably below the Personal Social Services Research Unit cost of patient journeys which, if used, would have increased the cost of treatments requiring more than one visit (iron sucrose and ferric carboxymaltose at the 1600 mg dose level).

The ability to administer high doses of intravenous iron rapidly, without the need for a test dose, is an important development in the strategy to reduce the use of blood, to improve the treatment, and avoid iron deficiency anemia. Ferric carboxymaltose, was the first intravenous iron to be introduced to the UK which did not require a test dose. Whilst it can be given rapidly, it can be administered at a maximum of 15 mg/kg body weight and to a ceiling of 1000 mg per infusion, limited to once a week. Iron isomaltoside 1000, whilst also administered rapidly, allows for 20 mg of iron per kg of body weight. This range of dosing offers a broader spectrum of treatment, including total dose infusions, for a potentially larger proportion of patients. This may be of particular importance when calculating the treatment dose based on the Ganzoni formula that includes replenishing body iron stores.[17] Doses for a number of disorders associated with iron deficiency anemia commonly require doses in excess of 1000 mg.[18–22] Patients requiring more than 1000 mg of iron will require more than one infusion of ferric carboxymaltose, necessitating two or more hospital or clinic visits.

Conclusion

Parenteral iron treatment has advanced significantly. Initially, ferric carboxymaltose offered the option of high-dose intravenous iron that could be administered in a short time span, and does not require a test dose, but is limited to 15 mg/kg body weight up to a maximum of 1000 mg in a single administration. This has been followed by the introduction of iron isomaltoside 1000 which likewise does not require a test dose, can be given rapidly, and offers the scope of dosing at up to 20 mg/kg body weight.

In a cost-conscious health care environment, the relative holistic cost of administering these new formulations has to be considered when making prescribing policy decisions. This cost minimization study indicates that savings can accrue by adopting iron isomaltoside 1000 when compared with current standard practice (iron sucrose or blood) at three dose levels. It is less expensive than using ferric carboxymaltose at the three dose levels, ie, 600 mg, 1000 mg, and 1600 mg. Whilst in the modeling, low-molecular-weight iron dextran is marginally cheaper to administer at the 1600 mg dose level (but not at the 600 mg or 1000 mg levels), the

time to administer this formulation takes six hours, thereby restricting patient throughput and the number of patients treated, and affecting unit efficiency. Low-molecular-weight iron dextran is also less convenient for patients.

It is acknowledged that there are limitations to the analysis, as detailed in the discussion. Such an analysis cannot be absolutely comprehensive in considering all costs applicable in all units. These are dependent on the availability of alternative preparations to a unit to choose from, desired clinical outcomes (eg, target hemoglobin and ferritin levels) and facilities. Clearly, staff time and transportation are important dynamics in the context of a comprehensive cost analysis, but are often omitted, resulting in the unit cost of the medication becoming the sole factor for decision-making.

This analysis suggests that iron isomaltoside 1000 is a convenient and more cost-effective intravenous iron treatment for iron deficiency anemia than the current most widely prescribed intravenous iron, ie, iron sucrose, or a blood transfusion in clinical situations where high-dose iron repletion is clinically appropriate. This may be particularly important in the strategy of reducing blood use and reducing the incidence and volume of blood transfusions in the UK.

Disclosure

The author reports no conflict of interest in this work.

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