

Route of Administration for Erythropoiesis-Stimulating Agents: Patient and Nursing Considerations

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Epoetin alfa is typically administered by the intravenous (IV) route for patients on hemodialysis and by the subcutaneous (SC) route for patients on peritoneal dialysis. Using the IV route for patients on hemodialysis avoids the need for additional needle sticks, enhances patient comfort, and provides a staff-convenient thrice-weekly dosing schedule. In addition, the Epoetin alfa prescribing information that has been approved by the Food and Drug Administration recommends the IV route for patients on hemodialysis due to the warning of an increased risk of pure red cell aplasia associated with SC administration. Conversely, SC administration is more convenient for patients on peritoneal dialysis, because they do not have a ready vascular access and typically self-administer Epoetin alfa at home. While either route can yield equivalent hemoglobin (Hb) results, there is an ongoing debate over whether the SC route may allow lower doses of Epoetin alfa. The many studies that have examined this topic over the past two decades have yielded divergent results, with some authors reporting dose reductions in patients who were switched from the IV to the SC route, and others finding that patients require either an increase or no change in the dose (Ashai, Paganini, & Wilson, 1993; Jacobs, Frei, & Perkins, 2005; Kaufman & Reda, 1996; Pizzarelli, David, Sala, Icardi, & Casani, 2006).

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Several clinical studies have indicated that compared with intravenous (IV) administration, subcutaneous (SC) administration of Epoetin alfa may result in a dose-sparing effect in patients on hemodialysis. However, data also indicate wide inter-patient variability in response, with many patients requiring the same or a higher dose following conversion to SC administration. Convenience favors IV administration of Epoetin alfa in patients on hemodialysis, and patient preferences and comfort should also be primary considerations. For patients who prefer SC injections, the nurse's coordination of the required dosing, administration, and operational factors is key to maintaining and improving anemia-related outcomes.

This article provides a brief overview of the literature comparing the IV and SC routes in adult patients on hemodialysis, with a focus on the patient and nursing factors that should be considered when determining whether IV or SC administration is appropriate for a particular patient.

Clinical Study Results

Differences in study design and methodology make it difficult to compare data from studies analyzing the use of IV versus SC Epoetin alfa. Although several analyses that were published in the 1990s reported lower doses with SC Epoetin alfa than IV administration, an analysis of these data reveals many flaws in study designs as well as inconsistent findings, thus rendering their conclusions unreliable. Critiques of these studies identified several criteria needed for an accurate comparison, including (a) a large study size to account for differences in patient response, (b) a washout or stabilization period to allow the effects of the previous route to dissipate, (c) a selection process that evaluates IV and SC doses in the same patient, (d) consistent levels of iron, (e) enough time for the Hb to stabilize after changes in the dose or route of administration, and (f) a study design that evaluates the potential effects of erythroid hyperplasia (for example, dose reductions may also be possible in patients receiving stable doses by either the IV or SC routes)

(Ashai et al., 1993; Jensen, Madsen, & Jensen, 1996; Paganini et al., 1995; Pizzarelli et al., 2006).

Unfortunately, most of the studies on this topic fall short on one or more of these criteria, and recent studies have shown that some of the inter-patient variability attributed to the route of administration may also be caused by individual patient characteristics. For example, a cross-sectional analysis performed by the European Survey of Anemia Management of 6,056 patients from 12 countries found that differences in dose requirements between the IV and SC routes of administration in patients on hemodialysis depended on patient's mean Hb level. Among patients with Hb concentrations below 11 g/dL, the dose was 11.8% higher for IV administration than for SC administration ($p = 0.016$). By contrast, Epoetin doses were 2.5% lower for IV administration among patients whose Hb was at least 11 g/dL ($p = \text{NS}$) (Jacobs, Frei, & Perkins, 2005).

Similarly, several studies have suggested that iron status may have a significant impact on Epoetin alfa dose requirements, and that IV and SC doses may not be significantly different in patients who are iron replete (De Schoenmakere et al., 1998; Leikis, Kent, Becker, & McMahon, 2004; Taylor, Peat, Porter, & Morgan 1996). To test this theory, a multicenter, prospective study was conducted with 265 patients receiving hemodialysis; patients maintained on SC Epoetin

were switched to an identical dose administered intravenously. The study protocol required patients to be iron replete during both phases of therapy: ferritin was 454 ± 237 ng/mL and 397 ± 195 ng/mL, while transferrin saturation was $30.9\% \pm 10.2\%$ and $30.5\% \pm 10.8\%$ during the SC and IV phases, respectively (Pizzarelli et al, 2006).

Results revealed no significant difference in Hb values following conversion to the IV route: Hb was 11.49 ± 0.76 g/dL during SC therapy, and 11.44 ± 0.79 g/dL during the IV phase ($p=0.194$). Similarly, there was no significant difference in dose requirements when Epoetin was administered by the SC and IV routes. Although doses tended to decrease following conversion from SC to IV administration in those requiring 12,000 units/week or more at baseline, cumulative doses were similar in both phases: $28,740 \pm 18,364$ units/month during the SC phase, and $29,081 \pm 19,817$ units/month during the IV phase ($p=NS$) (Pizzarelli et al., 2006).

The Kidney Disease Outcomes Quality Initiative (KDOQI™) performed an evaluation that attempted to account for study design. The single large, multicenter, randomized control trial that has been published on the route of administration provides enough evidence to support the statement that SC administration of Epoetin alfa is typically more efficient than IV administration (National Kidney Foundation, 2006). In this study by the Department of Veterans Affairs of 208 patients on hemodialysis, Hb levels were first allowed to fall below 10 g/dL before patients were randomized to receive IV or SC Epoetin alfa three times a week. The dose was then increased by 30 Units/kg/week every 4 weeks until the Hb was at least 10 g/dL for 2 consecutive weeks, and doses were subsequently adjusted over a 26-week maintenance phase to maintain Hb between 10 and 11 g/dL (Kaufman et al. 1998).

Among patients who completed the 26-week maintenance period, the average weekly dose needed to maintain Hb in that range was 27% lower in patients who received SC Epoetin

Table 1
Candidates for IV and SC Administration of Epoetin alfa

Potential Candidates for IV Epoetin alfa	Potential Candidates for SC Epoetin alfa
<ul style="list-style-type: none"> • Patients who prefer IV administration • Patients on hemodialysis • Patients who are obese or who have a thick SC tissue layer • Patients requiring a dose of Epoetin alfa with a volume more than 1 mL • Patients who cannot tolerate SC injections • Patients in dialysis facilities where patient privacy and/or staffing constraints make routine SC administration impractical 	<ul style="list-style-type: none"> • Patients who prefer SC administration • Patients on peritoneal dialysis • Patients requiring a dose of Epoetin alfa with a volume of 1 mL or less (e.g., those with residual renal function who still produce a significant amount of endogenous erythropoietin) • Patients on hemodialysis less than 3 times a week

alfa than in those treated by the IV route ($p = 0.0001$). However, there was significant inter-patient variation in dose requirements. Among patients who switched from IV to SC administration, 58% experienced a decrease in dose, and 42% required either an increase or no change. Similarly, among those who switched from SC to IV administration, 49% required an increase in dose, while 51% either required no change or experienced a decrease. While these results suggest that SC administration may be more efficient for some patients, they also highlight significant inter-patient variability in response and indicate that many patients may require the same dose or a higher one when converting from IV to SC Epoetin alfa (Kaufman et al., 1998).

Subsequent analyses of clinical practices have provided additional insights and confirmed the wide inter-patient variability in response to SC administration. An analysis of 7,658 randomly chosen patients by the United States' End-Stage Renal Disease Core Indicators Project assessed the impact of the SC and IV routes of administration in clinical practice (rather than in a study setting). After controlling for Hb, patient characteristics, iron status, adequacy of dialysis, serum albumin, postdialysis weight, and duration of dialysis, the average dose of Epoetin alfa in patients on dialysis was about 14% lower in those receiving the drug sub-

cutaneously than in those receiving it intravenously (McClellan et al., 2001).

In combination, these data indicate significant interpatient variability in the response to SC Epoetin alfa. While some patients may experience a decrease in dose to achieve an equivalent Hb, others require the same dose or an increase in dose.

Patient Considerations for SC Administration of Epoetin alfa

Since administration of Epoetin alfa by either the IV or the SC routes results in similar efficacy in patients on hemodialysis, the decision as to whether SC administration is right for a patient should be based on patient preferences and individual characteristics (see Table 1). Patient preference, comfort, and quality of life should be the primary considerations when assessing the advisability of converting to the SC route. While most patients on hemodialysis prefer receiving Epoetin alfa by the IV route, data indicate heterogeneity in patients' acceptance of SC injections. The Kaufman and Reda study (1996) referenced by KDOQI™ found that 86.4% of patients who were switched from SC injections to IV preferred IV, while only 10.7% preferred SC and 9.1% had no preference. Similarly, among patients switched from IV to SC injections, 57.1% preferred IV, 10.7% preferred SC, and 32.1% had no preference (National Kidney Foundation, 2006).

A more recent evaluation of patient preferences by the Renal Support Network (2007) found similar results. This national organization of patients with chronic kidney disease conducted a survey to determine patients' opinions on a broad range of issues. As part of this survey, patients were asked about their involvement in decisions on route of administration and whether they preferred that erythropoiesis-stimulating agents such as Epoetin alfa be administered by the IV or SC routes. Results from 828 respondents revealed that 85% believed that the method of administering a medication should be a decision made jointly by the patient and the physician. Among patients currently or previously receiving hemodialysis ($n = 773$), 84% indicated that they preferred to have medications such as Epoetin alfa administered intravenously during the dialysis procedure, while only 5% preferred SC injections. These data confirm that the route of administration is important to patients on hemodialysis and that they want to be involved in decisions affecting their quality of life. In addition, although there is some heterogeneity in patient preferences, these analyses indicate that the vast majority of patients on hemodialysis do not want to receive unnecessary SC injections.

For those who prefer SC injections, patient-specific characteristics should be evaluated when considering whether converting to the SC route is appropriate. For example, data indicate that body mass may exert a significant effect on the response to SC administration, and patients whose body weight exceeds 90 kg (about 198 pounds) or whose lateral thigh skinfold thickness is greater than 20 mm (equivalent to a SC tissue layer of approximately 10 mm) have been shown to have a poorer response to SC administration than thinner patients (Brahm, 1999; Elston & Macdougall, 2000). As a result, obese patients or those with a thick SC tissue layer may not be the best candidates for SC administration.

The volume of the injection should be considered when determining

Table 2
Considerations Related to Dosing and Administration

- Patient response
- Patient privacy
- Patient comfort
- Patient preference
- Patient convenience
- Need for individualized dosing
- Number of SC administrations prescribed
- Frequency of Hb monitoring
- Monitoring Hb trends
- Frequency of Epoetin alfa dosing changes
- Missed doses
- Rotation of SC injection sites
- Method for tracking SC injection sites
- Avoidance of arm containing vascular access
- Condition of skin at site of SC injection
- Pain and injection site trauma
- Availability of various concentrations of Epoetin alfa that allow SC doses equal to or less than 1 mL

whether a patient is a candidate for SC administration. To ensure patient comfort, the volume of drug to be injected should typically not exceed 1 mL (Rushing, 2004). As a result, patients who require lower doses of Epoetin alfa – such as those with residual renal function and higher levels of endogenous erythropoietin production – may be potential candidates for SC administration. By contrast, patients requiring higher doses that would equate to a high injection volume may be candidates for the IV route.

Nursing Considerations for SC Administration of Epoetin alfa

Considerations Related to Dosing

Several patient issues need to be considered regarding the route of administration (see Table 2). These suggestions can be used to help ensure that anemia management protocols contain appropriate guidelines for the use of IV and SC Epoetin alfa.

Many of the clinical trials comparing SC and IV administration have arbitrarily reduced the dose when switching from IV to SC injections. However, since up to 50% of patients require the same or a higher dose of SC

Epoetin alfa compared with the IV route, an individualized dosing approach is recommended. Therefore, to avoid a potential change in Hb when switching to SC administration, it may be prudent to maintain the same dose and dosing frequency for about one red cell life cycle (60 to 90 days) and monitor Hb closely. For example, a patient receiving 6,000 units three times a week intravenously could initially be switched to 6,000 units subcutaneously three times a week.

Following the conversion, the dose can be titrated upward or downward and the frequency of administration can be adjusted depending on the individual response. To allow adequate evaluation of the response to the change in route and/or frequency of administration, a change in dose should typically not be prescribed more frequently than once every 4 weeks (Amgen, 2007). When longitudinal trends in the Hb dictate the need for a change in the prescription, the Epoetin alfa dose should be titrated in increments or decrements of approximately 25%. After any change in the dose or the frequency of administration, or when the Hb is rising or falling, longitudinal trends in Hb values should be monitored frequently to assess how the modification affects the Hb response.

The anemia management protocol should also include provisions for handling missed doses. The KDOQI™ recommendation that a missed dose be replaced at the earliest possible opportunity is fairly straightforward for patients who are on hemodialysis and receiving IV Epoetin alfa three times a week. However, this recommendation may present challenges for a patient receiving SC injections. For those receiving thrice-weekly SC injections, the need to replace a missed dose may result in a total volume of administration that is greater than 1 mL if the total dose is greater than 10,000 Units and the dialysis facility stocks 10,000 Units/mL vials (as is common practice). In such cases, one approach that may help improve patient comfort is to divide the dose into two injections so that neither exceeds 1 mL. When a patient misses an injection, it results in a delay in therapy that can be prolonged if the missed dose occurred during the long interdialytic period.

Considerations Related to Administration

Subcutaneous administration of Epoetin alfa in patients on hemodialysis may require modification of the anemia management protocol (see Table 2). For example, the protocol should include a policy on how to rotate and track SC injection sites.

Rotating injection sites is important to avoid scarring or keloid formation, which can lead to decreased drug absorption. SC injections should be preferentially administered in the areas of the body with the most SC tissue, such as the abdomen, posterior upper arm, anterior and lateral thigh, and buttocks. However, it is generally recommended that SC injections not be administered in the arm that has the vascular access. Administration in the other arm may be acceptable unless it is being preserved or prepared for a revised vascular access. Using a SC site rotation chart to vary injection sites within the same anatomic region rather than between different regions is recommended because it may help diminish varia-

tions in drug absorption. At the time the SC injection is administered, it is also important for the nurse to carefully inspect potential sites and avoid areas with stretch marks, edema, scars, lipohypertrophy (a concave or pitted appearance of the skin, that may be more prevalent in patients who have diabetes and are receiving SC insulin), and other skin changes that may affect the absorption of subcutaneously administered drugs (Registered Nurses Association of Ontario, 2004).

Tracking SC injection sites is vital in patients who receive ongoing injections, and it can be especially challenging in patients who have diabetes and are self-administering insulin and are also receiving SC Epoetin alfa. In such patients, nurses must work in partnership with the patient, who should maintain a detailed insulin injection site chart that is brought to the dialysis facility for the nurse to review prior to administering each SC Epoetin alfa injection. It is also important that the site of injection be documented in the medical record – documentation requirements may vary based on individual state regulations.

Another consideration – injection site pain – can often be modified by choosing an appropriate concentration to limit injection volume (1 mL or less is recommended), bringing the vial to room temperature before administration, applying ice to the site before the injection, using a slow rate of injection, using a small-gauge needle, and avoiding leakage of Epoetin alfa on the needle or needle tip. Using a multidose vial (which contains benzyl alcohol as a preservative and acts as a local anesthetic) may also decrease pain and improve patient comfort.

Injection administration technique can also help ameliorate the pain that may be associated with SC administration of Epoetin alfa. The key to a comfortable injection is swift needle entry, followed by slow injection of fluid and quick withdrawal of the needle. Aspiration is not necessary following the insertion of the needle, since the likelihood of injecting into a blood vessel is small and aspiration

can cause tissue damage, hematoma formation, and bruising. The patient should also be advised not to massage the site following injection, since trauma can result in damage to the underlying tissue and cause the medication to be absorbed faster than intended (Rushing, 2004). It is important that nurses ensure that injections are not unintentionally administered intradermally. This can sometimes occur when those who are concerned about injecting too deeply and entering the muscle inadvertently inject the drug intradermally. This is painful and moreover is associated with poor drug absorption. Although these measures can often make the SC route more palatable for patients, nurses should be aware that some patients may find SC administration intolerable after a reasonable trial period and that a switch back to IV administration may be warranted.

Finally, nurses also need to consider the setting in which the SC injection will be administered. The need for ongoing site rotation and for preserving the integrity of the vasculature means that SC injections are often administered in the abdomen or legs. As a result, depending on the layout of the facility, patient privacy may need to be considered. To avoid potential embarrassment on the part of the patient at having to partially disrobe in public while in the dialysis chair, facilities may need to consider using a privacy screen, or administering SC injections in a private area either before or after dialysis. Finally, since SC Epoetin alfa injections need to be administered by licensed personnel, nurses will need to plan when in the course of the dialysis session they will administer the injection, based on both their workload and the patient's preferences.

Conclusions

IV administration of Epoetin alfa is preferred for patients on hemodialysis due to the availability of a ready vascular access, patient preferences, and the wide range of operational challenges inherent in ongoing SC

administration. Although convenience favors IV administration for most patients on hemodialysis, some facilities may prefer SC administration. The decision should be made on an individual patient basis. In such cases, nurses should be empowered to assess and manage the specialized dosing and administration techniques required to ensure and improve anemia-related outcomes.

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