Intravenous apomorphine therapy in Parkinson’s disease
Clinical and pharmacokinetic observations

A. J. Manson,¹,² H. Hanagasi,¹,² K. Turner,¹,² P. N. Patsalos,³ P. Carey,⁴ N. Ratnaraj⁵ and A. J. Lees¹,²

¹The Reta Lila Weston Institute for Neurological Studies, The Middlesex Hospital, ²The National Hospital for Neurology and Neurosurgery, ³Institute of Neurology, London and ⁴Harefield Hospital, Middlesex, UK
Correspondence to: Professor A. Lees, The Reta Lila Weston Institute for Neurological Studies, The Windeyer Building, 46 Cleveland Street, London W1P, UK
E-mail: alees@ion.ucl.ac.uk

Summary
Six patients with Parkinson’s disease and refractory motor fluctuations, with severe subcutaneous (s.c.) nodule formation as a result of long-term s.c. apomorphine infusions, were switched to intravenous (i.v.) therapy via a long-term in-dwelling venous catheter. Five patients were followed-up for a mean of 7 months (range 0.5–18 months). All patients had plasma apomorphine concentrations measured at baseline during s.c. infusions and three had follow-up measurements when stabilized on i.v. therapy, to test the hypothesis that motor fluctuations in these patients are largely due to impaired absorption of apomorphine. The mean i.v. rate of 9.0 mg/h (range 5–14 mg) and 24-h dose of 256.7 mg (range 90–456 mg) of apomorphine were not significantly reduced compared with the s.c. route (9.24 mg/h and 243.4 mg). However, additional oral anti-parkinsonian medication was reduced by a mean of 59%, and ‘off’ time was virtually eliminated (mean reduction from 5.4 to 0.5 h per day, P < 0.05). There was also a significant reduction in dyskinesias and markedly improved quality of life. Pharmacokinetic analysis demonstrated more reliable and smoother delivery of apomorphine via the i.v. route, although ‘off’ periods were not always explained by low plasma apomorphine concentrations. Complication rates were high and included three unforeseen hazardous intravascular thrombotic complications, secondary to apomorphine crystal accumulation, necessitating cardiothoracic surgery. We conclude that i.v. apomorphine therapy holds promise as a more effective way of controlling motor fluctuations than the s.c. route. However, further preclinical research is required before i.v. Britaject apomorphine can be recommended for routine clinical practice. Even when stable plasma apomorphine concentrations were achieved, motor fluctuations could not be totally eradicated, suggesting that postsynaptic receptor changes may also play a role in the refractory ‘off’ periods in these patients.

Keywords: apomorphine; Parkinson’s disease; central venous catheter, intravenous

Abbreviations: i.v. = intravenous; s.c. = subcutaneous

Introduction
Subcutaneous (s.c.) infusions of apomorphine have been shown to improve the refractory motor complications of late-stage Parkinson’s disease, reducing ‘off’ time by at least 50% (Chaudhuri et al., 1988; Frankel et al., 1990; Hughes et al., 1993; Colosimo et al., 1994; Pietz et al., 1998), and, when used as monotherapy, to markedly reduce levodopa-induced dyskinesia (Colzi et al., 1998; Kanovsky, 1999). Unfortunately, with long-term use, skin complications, particularly s.c. nodule formation, commonly develop (Colosimo et al., 1994; Pietz et al., 1998). These occur to some degree in the majority of patients treated chronically with s.c. apomorphine infusions (Pollak et al., 1993; Wenning et al., 1999); they are moderate to severe in over 50% (Colzi et al., 1998), but are only severe enough to cause major clinical problems in a minority (10% of our patients on s.c. infusions for ≥3 years). Histologically, the nodules consist of a focal panniculitis, without systemic eosinophilia, which could be due to a hypersensitivity reaction to either the apomorphine or the metabisulphite preservative, but the histopathology of the nodules is poorly understood; therefore prophylactic and treatment strategies are limited (Acland et al., 1998). However, the use of dilute solutions of apomorphine (using 50% normal saline with the infusion) and the application of a silicone gel patch and local ultrasound or massage treatment have all been used, with some success, to try to minimize the problem (Lees, 1993; Colzi et al., 1998).
and performed a pharmacokinetic study to investigate whether the difference in efficacy was due to impaired absorption via the s.c. route.

Patients and methods
Seven patients (four men and three women) with idiopathic Parkinson’s disease, a mean age of 56.5 years (range 49–75 years) and a mean duration of disease of 14.7 years, who had received s.c. infusions of apomorphine for a mean of 4.2 years, were selected. Approval for the study was granted by the Chairman of the University College Hospital Medical School Ethics Committee. All patients had had an excellent initial response to s.c. apomorphine but had developed extensive s.c. nodules, compromising the long-term therapeutic response. All had been given optimum oral anti-parkinsonian medication, including high-dose dopamine agonists (including, in two patients, the long-acting preparation cabergoline) and COMT (catechol O-methyltransferase) inhibitors (which were withdrawn on switching to i.v. therapy). Two of the patients (Patients 1 and 5) were receiving 24-h s.c. infusions of apomorphine, but required additional bolus injections as well as oral anti-parkinsonian medication. Patient 2 had reduced the hours of s.c. infusion to less than 12 per 24 h to try to minimize skin complications and reduction in efficacy, and was relying on hourly s.c. bolus injections of apomorphine for the rest of the time. Patient 3 had abandoned the use of the s.c. infusion a month previously due to skin complications and reduction in efficacy, and was relying on hourly s.c. bolus injections of apomorphine and oral anti-parkinsonian medication. Patients 4 and 6 were on waking-day infusions, but had needed to introduce additional bolus rescue injections of apomorphine as well as oral anti-parkinsonian medication throughout the day for symptom control. All patients filled in diary cards to evaluate motor fluctuations before initiation of i.v. therapy. Patients who did not demonstrate significant unpredictability of motor response during the s.c. infusion assessment and had active inflammatory bowel disease, was deemed unsuitable for i.v. therapy. Six patients, who gave informed consent according to the Declaration of Helsinki, went on to have a portacath inserted under light sedation. The procedure was performed by a qualified surgeon or anaesthetist. All patients had an electrocardiogram, basic biochemistry, haematology and thrombophilia screens before catheter insertion, and were given 300 mg aspirin, or low-dose warfarin, daily once the portacath was inserted. The infusion line was changed every 48 h and the portacath needle was replaced, and the catheter flushed with heparinized saline every 2 weeks. Follow-up

1996; Kock et al., 1996) and are totally implantable, and therefore less susceptible to infection than Hickman lines, and allow multiple punctures for long-term use. We selected a small group of patients for i.v. apomorphine therapy who had responded excellently to s.c. infusions but who had severe nodule formation, and performed a pharmacokinetic study to investigate whether the difference in efficacy was due to impaired absorption via the s.c. route.
care of the catheter was provided by patients’ local haematology units and/or the authors (A.J.M. and K.T.), although patients and carers were encouraged to learn to care for the system independently. One patient and their carer were able to manage the system completely independently within 6 weeks of starting treatment and did not develop even minor localized infections during 18 months of treatment.

**Pharmacokinetic studies**
Serial plasma apomorphine concentrations were measured to determine whether the motor fluctuations experienced by these patients whilst on apomorphine were due to erratic absorption and plasma concentration falling below threshold. This was done during the patients’ day-case assessments before catheter insertion. Patients were asked to discontinue the apomorphine infusion for at least 8 h, unless they were on 24-h infusions, in which case they were asked to stop the infusion at least 50 min before assessment. All patients were assessed clinically at baseline in the ‘off’ state. The apomorphine infusion was then started and patients were asked to continue their normal medication routine. They were allowed to alter the infusion rate, or have an additional s.c. injection of apomorphine, if they felt they were going ‘off’. A 22-gauge i.v. cannula was inserted into the forearm, from which serial blood samples were taken for assessment of apomorphine plasma concentration. Blood samples were taken at baseline, in the ‘off’ state and then at increasing intervals (two 5-min intervals, two 10-min intervals, and then 20-min intervals) after the infusion was started, and after any change in rate or bolus rescue dose. Once a steady clinical ‘on’ state had been achieved, samples were taken every 30–40 min. Patients gave subjective impressions of their motor state (which was considered an important factor, as it often dictates self-regulation of medication) and were assessed clinically (by A.J.M. and H.H.) for signs of worsening of parkinsonism (marked increase in tremor, rigidity and bradykinesia) before each blood sample was taken. These features were combined to form a modified clinical global state scale, as follows: –1 = ‘off’, objectively and subjectively; –0.5 = patient subjectively ‘off’ but objectively not in full ‘off’ state; 0 = patient coming ‘on’ or going ‘off’ (intermediate threshold state); 0.5 = patient objectively on but subjectively feels not fully ‘on’; 1 = patient both objectively and subjectively fully ‘on’; 1.5 = patient both objectively (excess dyskinesias, or confusion) and subjectively (light-headed, confused) overdosed.

**Apomorphine assay**
Plasma apomorphine concentrations were determined by high-performance liquid chromatography. The instrument comprised an automated Gilson system (Anachem) and a Spectra Physics FL 2000 fluorescence detector set at 270 nm excitation and 450 nm emission. Chromatographic separation was achieved using a hypersil BDS-C18 (3 µm, 125×3 mm) column (Hewlett Packard). Plasma samples were prepared for analysis as follows: 600 µl plasma was pipetted into a 2-ml plastic tube to which was added 600 µl ethyl acetate and the sample was vortex-mixed for 5 min. After centrifuging the mixture for 5 min, the upper ethyl acetate extract was transferred to a 1.5 ml plastic tube and 100 µl of 0.1 M HCl was added. After further vortex-mixing (5 min) and centrifugation (5 min), 90 µl of the aqueous layer was transferred into an autosampler vial, from which 10 µl was injected automatically into the chromatogram.

**Data analysis**
Data were tested for normality using the Shapiro–Wilk test. Means were compared using Student’s and Wilcoxon’s tests appropriately. Correlations between clinical ratings and plasma apomorphine concentrations were assessed with Pearson’s coefficient.

**Results**
Five patients were followed-up for a mean of 7 months (range 0.5–18 months). One patient developed a postoperative line infection, necessitating its removal within 2 weeks of insertion, before follow-up data could be collected. The mean i.v. rate of 9.0 mg/h (range 5–14 mg/h) and 24-h dose of 256.7 (90–456) mg of apomorphine were not significantly reduced compared with the s.c. route (9.24 mg/h and 243.4 mg/24 h, respectively). However, two patients were able to run the i.v. infusions for nearly double the number of hours each day compared with patients using the s.c. route. Also, patients no longer needed to take additional bolus rescue injections of apomorphine, although, if they felt an impending ‘off’ period, they would make use of the boost function on the pump, which would quickly bring them back ‘on’ again, usually within 1 or 2 min. The mean number of i.v. boosts per day during i.v. infusion was 4, with a mean dose per boost of 2.2 mg, whereas the mean number of extra s.c. injections during s.c. infusion was 11.2, with a mean dose of 7.2 mg. There was a mean (standard deviation) reduction in additional antiparkinsonian medication of 59% (42%), including a 58% mean reduction in daily levodopa from a mean of 450 mg to 183 mg (P = 0.068). ‘Off’ time was almost eliminated, with a mean (standard deviation) individual reduction of 88% (41%), from a mean daily total of 5.4 h to 0.5 h, P < 0.05. Although not formally assessed as a primary outcome, there was also a reported significant reduction in dyskinesias, which was marked in one patient, who had experienced severe dyskinesias when on s.c. infusion plus oral levodopa and additional bolus injections. Within 2 days of i.v. therapy, however, he was able to return to apomorphine monotherapy with a dramatic reduction in dyskinesias. Patients also reported a marked improvement in general well-being and quality of life, although the number of patients was too small to allow formal measurement. However, patients made comments such as ‘I don’t feel like
Fig. 2 Patient 1. Plasma apomorphine concentration and simultaneous clinical state during s.c. infusion at 14 mg/h (A) and i.v. infusion at 15 mg/h (B), demonstrating erratic and unreliable response to s.c. infusion and numerous 8-mg bolus injections compared with the smoother and predictable response to i.v. infusion and bolus doses (arrows). All infusions commenced at time = 0. Filled diamonds = plasma apomorphine concentration; open squares = clinical state. Arrows represent apomorphine boluses.

I’ve got Parkinson’s disease any more’. On a more practical note, however, patients reported that they were able to do far more, including activities such as going to the theatre and taking the dog for a walk, which they had not felt able to do for many years previously.

Pharmacokinetic studies
The within- and between-batch precision for the determination of plasma apomorphine over the concentration range 75–399 µg/ml was determined. The coefficient of variation for within-batch precision varied from 2.0 to 3.8%, while that for between-batch precision varied from 1.9 to 5.6%.

Pharmacokinetic data during s.c. infusions were obtained from all seven patients. Three (Patients 1, 2 and 3) had later follow-up assessments during i.v. infusions (Figs 2–4), and four (Patients 4–7), who had stopped treatment before follow-up studies could be arranged (for the reasons listed above), had baseline studies only (Fig. 5). Before starting the i.v. infusion, Patient 1 had the portacath needle changed, which resulted in a large bolus of apomorphine being given; this was reflected in both the plasma apomorphine concentrations and clinical state (Fig. 2). Figure 2 demonstrates the erratic and unreliable response to s.c. infusion and numerous 8-mg bolus injections compared with the smoother and predictable response to i.v. infusion and bolus doses.

After 250 min of the i.v. infusion, Patient 2 felt himself to be going ‘off’ and then noticed that the syringe had run out of apomorphine; the syringe was therefore changed and treatment was restarted with a small bolus of apomorphine (Fig. 3). Compared with the s.c. route, there was less variability in plasma apomorphine concentration during i.v. infusion, except when the syringe ran out (Fig. 3). Patient 3, who had not been using s.c. infusion for 1 month before assessment, did not experience motor fluctuations during the assessments, but demonstrated steadier plasma apomorphine concentrations and clinical state during i.v. infusion.

Figures 2A and 5 demonstrate the erratic and unreliable response to infusion and s.c. bolus doses for Patients 1, 4, 5, 6 and 7. After 135 min, Patient 7 increased the rate of s.c. infusion from 2.5 to 3 mg/h (Fig. 5), as the lower dose had not succeeded in switching her fully ‘on’.

Clinical response and plasma concentrations of apomorphine after i.v. administration of apomorphine were much more predictable than after s.c. administration. Intravenous boosts of apomorphine were also better at turning a patient back ‘on’ than s.c. bolus injections.

There was no direct correlation between simultaneous plasma apomorphine level and clinical state during s.c. or
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formed at the catheter tip. This was discovered after the patient complained of an increase in apomorphine requirement and shortly after, the mass embolized to the right lung, requiring surgical removal. The patient made a good recovery and returned to s.c. therapy. The second patient, who had been on i.v. therapy for 6 months, had been experiencing domestic problems, and had overdosed on a bolus of >250 mg, after which he was found to have superior vena cava obstruction and an atrial mass, which was surgically removed. The patient stated that the overdose had been a ‘cry for help’ rather than a genuine suicide attempt. As with the first patient, even when aware of the dangers of continuing i.v. apomorphine, he expressed a strong desire to continue but he was persuaded to return to s.c. therapy. Other adverse events were typical of indwelling central venous catheters, and included postoperative wound infection \( n = 2 \), venous thrombosis \( n = 1 \), translocation of the catheter tip into the external jugular vein \( n = 1 \) and localized skin pocket infection \( n = 4 \). There were three catheter resitings, as a result of complications; two of these were with a Hickman line instead of the portacath. The Hickman lines produced a good clinical effect but were subject to frequent infections, which necessitated removal in both patients in less than 2 months. Three patients strongly requested to continue with the i.v. therapy because of their marked subjective improvement in quality of life, despite being fully informed of the potential risks.

Patients on i.v. therapy required a great deal of back-up support, with a mean of about five telephone calls and one visit per patient per week being made to the specialist nurse or research fellow.

**Adverse events**

Despite cautious monitoring, two patients, on very high doses of apomorphine (450 and 290 mg/24 h), experienced unforeseen, hazardous intravascular thrombotic complications, requiring open cardiothoracic surgery on three occasions. These were assumed to be secondary to crystallization of apomorphine, acting as a nidus for thrombus aggregation. The first patient, who had received undiluted apomorphine (10 mg/ml) i.v. for 9 months, developed a large apomorphine/thrombus-containing mass at the end of the catheter tip, after 9 months of treatment. This extended into the right atrium, and was surgically removed without complications (Fig. 6). Despite medical advice, the patient and spouse insisted on continuing i.v. therapy. It was hoped the complication could be avoided by prophylactic measures, such as diluting the apomorphine to 5 mg/ml, flushing the catheter with heparinized saline every 48 h, giving prophylactic warfarin, and careful monitoring. However, after a further 9-month treatment period, with 3-monthly cardiological follow-up with echocardiograms and radioisotope imaging of the catheter tip, another smaller mass

**Discussion**

**Motor improvement**

Continuous dopaminergic stimulation by s.c. infusion has already been shown to improve motor fluctuations and dyskinesias markedly in Parkinson’s disease (Obeso et al., 1986; Poewe et al., 1993; Stocchi et al., 1997; Colzi et al., 1998; Pietz et al., 1998). The i.v. route offers a possible alternative approach to prolonging the efficacy of continuous apomorphine infusions in patients who have developed severe subcutaneous nodules after long-term therapy. Continuous enteral or i.v. infusions of levodopa have been shown to greatly reduce but not completely eradicate motor fluctuations (Hardie et al., 1984; Sage et al., 1989b). The presence of fluctuations despite i.v. levodopa infusions has, in part, been explained by the complex pharmacokinetics and pharmacodynamics of the drug (Nutt et al., 1984, 1997), possibly impairing delivery of levodopa to the brain from the periphery. Apomorphine, however, crosses the blood–brain barrier rapidly and easily and acts directly on postsynaptic receptors (Neef and van Laar, 1999). It is possible that the ‘off’ periods experienced by this group of patients on long-term s.c. apomorphine can be explained
partly by erratic absorption. However, the ‘offs’ demonstrated by our patients in the absence of falls in plasma apomorphine concentration would have to be accounted for by postsynaptic changes (Verhagen Metman et al., 1997). The repeated bolus injections of apomorphine required by patients whilst on s.c. infusions may also have contributed to increasing motor fluctuations due to pharmacodynamic changes (Grandas and Obeso, 1989). Another explanation for the superior efficacy of i.v. infusion in these patients could be a more rapid effect of the i.v. boost function, which may have avoided full establishment of ‘off’ periods.

The improvement in dyskinesias seen in our patients supports the idea that dyskinesias arise from an imbalance in neuropeptide expression and receptor activity in the direct and indirect pathways (Piccini et al., 1997) and the interconnecting circuitry of the basal ganglia, which can be ‘reset’ (Sage and Mark, 1992; Brotchie, 1998) by strategies such as returning to continuous tonic dopamine receptor stimulation (Sage et al., 1989a; Colzi et al., 1998). Indeed, although dopamine agonists have been shown to have a much lower proclivity to produce dyskinesias (Lees and Stern, 1981), preclinical studies suggest this may not be due to differences in dopamine receptor subtype stimulation (Bedard et al., 1992; Blanchet et al., 1993; Luquin et al., 1994) and, in any case, some dopamine agonists have pharmacological properties relating to D1, D2 and D3 stimulation, very similar to levodopa. A more plausible explanation is that the more prolonged action of many agonists leads to more tonic physiological stimulation of dopamine receptors (Facca and Sanchez-Ramos, 1996), which may account for this difference (Chase et al., 1989). Indeed, animal studies using continual as opposed to intermittent levodopa therapy have come close to normalizing this imbalance of neuropeptide expression in the striatal output pathways of 6-OH-dopamine-treated rats (Engber et al., 1989). In the past, plasma levodopa concentration has sometimes, but not always, been correlated with the presence and severity of dyskinesias (Rinne et al., 1973; Tolosa et al., 1975). However, although all our patients had a very narrow therapeutic window, generally expressing an all-or-nothing response to apomorphine, they were nearly always able to identify overdosing correctly, which was reflected by excessive dyskinesia and was closely related to an increase in plasma apomorphine concentration.

Fig. 5 Plasma apomorphine concentration and simultaneous clinical state during s.c. infusion for Patients 4–7, demonstrating erratic and unreliable response to infusion and s.c. bolus doses. All infusions commenced at time = 0. (A) Patient 4: infusion rate 10 mg/h, bolus dose 6 mg. (B) Patient 5: infusion rate 6.7 mg/h, bolus dose 4 mg. (C) Patient 6: infusion rate 5 mg/h, bolus dose 4 mg. (D) Patient 7: infusion rate 2.5 mg/h, increased after 135 min (dotted arrow) to 3 mg/h; bolus dose 1 mg. Filled diamonds = plasma apomorphine concentration; open squares = clinical state. Solid arrows represent apomorphine boluses.
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concentrations than had been required during s.c. therapy (Fig. 1), although the threshold values appeared unchanged (Figs 2–4). The slightly lower plasma apomorphine concentrations achieved during the i.v. infusion were considered to be secondary to the deposition of apomorphine crystals within the catheter rather than the result of peripheral tolerance or enzyme induction.

Complications

The complication rate in our patient group was unacceptably high. Stocchi and colleagues experienced similar minor complications (F. Stocchi, personal communication), such as localized skin infections \( n = 3 \), as well as one line infection, one venous thrombosis and four line occlusions, requiring catheter changes after 1 year (Stocchi et al., 1999b). Two of their patients were taken off treatment due to neuropsychiatric complications. One of the patients died of cardiac arrest, which was judged to have been unrelated to i.v. therapy. Although the lines tended to become occluded by apomorphine crystallization, requiring a change after ~1 year of use, the more serious problems that occurred in our study were not encountered, even though none of their patients was given anticoagulation treatment and the apomorphine solution was given at a higher concentration (10 mg/ml). There are two possible explanations for these differences: one is that the two patients in whom these masses accumulated were on much higher doses of apomorphine than the Italian patients, whose maximum 24-h requirement was \( 100 \) mg.

However, examination of a portacath (which was still patent and fully functional) removed from our patient who had been on \( 150 \) mg i.v. apomorphine per day for \( 4 \) months revealed accumulation of a black, apomorphine-containing, crystalline deposit at the catheter tip and within the lumen (Figs 7 and 8). The second possible explanation could be the slight variation in the apomorphine formulations used. Both the UK formulation (Britaject, manufactured by Britannia Pharmaceuticals, UK) and the Italian formulation (Chiesi Pharmaceuticals) contain apomorphine hydrochloride at 10 mg/ml, sodium metabisulphite as an antioxidant and buffering solutions as necessary. Although the study design did not allow formal pharmacokinetic calculations of \( C_{\text{max}} \) and the area under the curve, it could be seen that individual plasma concentrations did not correlate with individual apomorphine dosage. However, a large inter-subject variability in \( C_{\text{max}} \) and the area under the curve after apomorphine administration has been reported previously (Gancher et al., 1989). It has been suggested that tolerance to apomorphine may be related to duration of infusion (Gancher et al., 1996). As in previous follow-up studies (Hughes et al., 1993; Poewe et al., 1993; Gancher et al., 1995), our study did not demonstrate clinically relevant tolerance after long-term apomorphine infusion. In fact, the three patients followed up after 2–4 months of i.v. treatment for i.v. studies, two of whom were on 24-h infusions, maintained their ‘on’ states at slightly lower plasma concentrations than had been required during s.c. therapy (Fig. 1), although the threshold values appeared unchanged (Figs 2–4). The slightly lower plasma apomorphine concentrations achieved during the i.v. infusion were considered to be secondary to the deposition of apomorphine crystals within the catheter rather than the result of peripheral tolerance or enzyme induction.

Pharmacokinetics

Our pharmacokinetic studies show that the i.v. route is more efficient than the s.c. route in administering apomorphine effectively to patients with severe nodule formation. It was not surprising that the plasma apomorphine concentration did not correlate directly with the simultaneous clinical state, as there is known to be a lag of 10–20 min between plasma and CSF apomorphine concentrations (Hofstee et al., 1994; Przedborski et al., 1995; Neef and van Laar, 1999). Although the study design did not allow formal pharmacokinetic calculations of \( C_{\text{max}} \) and the area under the curve, it could be seen that individual plasma concentrations did not correlate with individual apomorphine dosage. However, a large inter-subject variability in \( C_{\text{max}} \) and the area under the curve after apomorphine administration has been reported previously (Gancher et al., 1989). It has been suggested that tolerance to apomorphine may be related to duration of infusion (Gancher et al., 1996). As in previous follow-up studies (Hughes et al., 1993; Poewe et al., 1993; Gancher et al., 1995), our study did not demonstrate clinically relevant tolerance after long-term apomorphine infusion. In fact, the three patients followed up after 2–4 months of i.v. treatment for i.v. studies, two of whom were on 24-h infusions, maintained their ‘on’ states at slightly lower plasma concentrations than had been required during s.c. therapy (Fig. 1), although the threshold values appeared unchanged (Figs 2–4). The slightly lower plasma apomorphine concentrations achieved during the i.v. infusion were considered to be secondary to the deposition of apomorphine crystals within the catheter rather than the result of peripheral tolerance or enzyme induction.

Clinical relevance

Intravenous apomorphine infusions resulted in almost complete elimination of ‘off’ periods and a reduction in dyskinesias in patients who had exhausted all other approaches of medical therapy. Although inclusion of a placebo control group in the study would have helped the interpretation of these results, it was not deemed to be a reasonable ethical consideration in such a study. A further
possible limitation of this study is that we did not report formal quality-of-life data. Whilst these data were collected for future reference, the sample size of 6 was considered too small to enable reliable and valid judgements at the individual patient level (McHorney and Tarlov, 1995; Hobart et al., 2000). The benefits of continuous apomorphine infusions are similar to those of stereotactic neurosurgical techniques, such as subthalamic nucleus deep brain stimulation (Krack et al., 1999). A further benefit, which we were not able to measure, could have been the avoidance of unpleasant mood fluctuations, known to be part of the ‘on/off’ phenomenon (Hardie et al., 1984). Therefore, even when the complication risks of i.v. therapy were explained, patients were extremely unwilling to return to s.c. infusions, and their wishes were usually reinforced by their carers. It could be argued that continuous apomorphine therapy was inducing a euphoric state or hedonistic homeostatic dysregulation, or impairing the patients’ judgement (Ruzicka et al., 1994; Giovannoni et al., 2000), leading to an unrealistically favourable subjective impression of improvement. However, the facts that apomorphine therapy has been shown to decrease neuropsychiatric complications of dopaminergic therapy in Parkinson’s disease (Ellis et al., 1997) and that the patients’ families and carers all agreed with the patients’ impression suggest that this is not an adequate explanation. The main benefit from i.v. therapy was related to increased confidence that the patients could avoid ‘off’ periods (fear of which often dominated their lives) and therefore lead an almost normal life.

We conclude that, although highly effective in smoothing the clinical response to apomorphine, i.v. Britaject is unsafe
due to potential deposition of apomorphine within the cardiovascular system, and its consequences. However, further preclinical research on apomorphine formulations is warranted.

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