Cutaneous side-effects of infused apomorphine: patient experience and effective management

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Abstract

Subcutaneously infused apomorphine, used in the treatment of Parkinson's Disease, is associated with the development of hard nodules at the infusion site. They may interfere with absorption of the drug and cause difficulty finding a suitable infusion site. Relatively little is known about aetiological factors for the development of the nodules, or about which treatments are found most effective.

A case series assessment was used to investigate nodule formation, effects and management in 24 individuals receiving apomorphine by infusion. Demographics and clinical information, opinions of patients and carers, and physical and sonographic assessment data were obtained.

Difficulty finding infusion sites was the most commonly reported problem caused by nodules. Tissue changes varied considerably, and included nodule formation, dermal thickening and diffuse oedema. No single factor was found to substantially influence severity, but poor hygiene and needle-changing technique appeared to exacerbate the problem. Various treatments were employed, and therapeutic ultrasound was reported particularly beneficial. Tissue evaluation by visual inspection, palpation and sonography may be feasible tools for the assessment of condition severity and treatment effectiveness.

Key words: Parkinson's Disease; apomorphine nodules; patient experience; assessment; treatment

Introduction

Apomorphine hydrochloride is used in the treatment of people with later stage Parkinson's Disease (PD), particularly those who are experiencing disabling "on-off" motor fluctuations (Tyne et al., 2004). It is administered subcutaneously, usually to the lower abdomen or thigh, by injection or continuous infusion (Lees and Turner, 2002). A common side effect is the development of subcutaneous nodules around the site of entry (Pietz et al., 1998, Hagell and Odin, 2001, Deleu et al., 2004). The nodules can be tender and they may become infected, necessitating antibiotic treatment or surgical debridement (Pietz et al., 1998). They may also create a barrier to absorption of the drug and so reduce its efficacy (Manson et al., 2001, Lees and Turner, 2002). Plasma apomorphine concentrations and Parkinsonian symptoms have been found to vary erratically when there is profuse nodule formation(Manson et al., 2001).

A majority of people on infused apomorphine develop nodules (Deleu et al., 2004). A new nodule may form every time the infusion needle is re-sited, which normally happens on a daily basis. Nodules may resolve with time but in some cases tissue becomes hardened over extensive areas, reducing the sites available for placing infusion needles and thus making nodule formation even more problematic.

Histological studies have concluded that apomorphine nodules are a form of panniculitis - a local inflammatory reaction in the subcutaneous tissue (Acland et al., 1998, van Laar et al., 1998). However there is little published work describing them, or concerning factors contributing to their development and resolution. Improved knowledge of causation and progression may provide a clearer rationale for the management of problematic cutaneous changes associated with the use of this drug.

The purpose of the present study was to describe the range of cutaneous and subcutaneous changes associated with the use of infused apomorphine, the factors that may impact on their development and resolution, and the perspectives of the people who are affected by them. The study took the form of a case series assessment.

Participants and methods

People receiving apomorphine for PD and experiencing nodule formation were recruited from the PD clinic of University College Hospital, London. All eligible patients were invited to participate. Information sheets were sent to all registering an interest, and informed written consent was obtained from those who were willing to take part. Of 27 people approached, 24 agreed to participate. The study protocol was approved by the institutional ethics committee and its scientific review panel.

Demographic and clinical information was gathered on participants from hospital notes, and assessments were carried out either during a routine outpatient check-up, on a home visit, or by telephone interview (2 people remote from the study site). Participants and their carers were interviewed to gain insights into their experience with nodules, the difficulties they caused, and management strategies adopted. Physical assessment was carried out using visual inspection and palpation. This was followed by sonographic imaging using a Sonosite Micromaxx System 3.4.1 with a 13-6 MHz linear array transducer (Sonosite Ltd, Hitchin, UK). Where possible, participants identified nodules as recently formed (within the previous few days) or longer-standing (several weeks or older). Nearby areas that were not used for infusion needle-siting were also assessed to obtain comparison data for unaffected tissue. The assessment was carried out jointly by a physiotherapist and a sonographer, and additional data was provided by the clinic's PD specialist nurse.

Qualitative data from participant and carer interviews was analysed to identify common features and differences. Demographic and medical history data were compared with measurements obtained from sonography, to investigate whether there were any associations between them.

Results

Demographic and clinical data for the participants are provided in table 1.

Table 1: Characteristics of study participants.

Parameter	values
Sample size	24
Sex	12 M, 12 F
Age / yr	65 (47-81)
Time since PD diagnosis / yr	20 (9-32)
Time on apomorphine / yr	6 (0.25-15)
Infusion rate / mg/hr	5.9 (3.25-13.75)
Infusion time / hr	14 (10-24)
Infusion dose / mg/day	79.5 (43.0-160)
Infusion site[a]	A=21 , T=8 , O=3

Values are given as mean (range); [a] A=abdomen; T=thigh; O=other sites (lower back and posterior shoulder). In some cases participants used several sites for infusion.

Nodule formation and associated problems

Nodule formation had been observed by most participants immediately or a few weeks after infusion treatment commenced. A nodule typically formed within hours of the infusion needle being removed, although sometimes no reaction was evident. Nodules would sometimes resolve within a few days or weeks, but a proportion lasted longer, some for months, and others gradually coalescing with others to form permanent hardened areas. For the majority of people experiencing significant nodule formation, the difficulty in finding useable infusion sites was cited as the most significant problem. As more areas become unusable, infusions are focussed in smaller areas and so cutaneous reactions occur closer together, exacerbating the problem. For some participants this was a source of anxiety as they anticipated a time when they would be unable to find a site for infusion: some had been forced to inject into tender or hardened tissue because they saw no other option, with consequent pain and the possibility of poor absorption of apomorphine. Pain or tenderness were reported by most participants, but in only one case was this regarded as a barrier to finding infusion sites. Nodules were usually at their most tender in their early stages of development, and occasionally became numb with age. Cosmetic appearance was not reported as of concern to any participant.

Prevention and management

All participants said they changed the infusion sites daily, usually alternating between left and right sides. However some – usually those who self-injected – tended to use comparatively small areas of the abdomen repeatedly, which meant that needle trauma and apomorphine reactions were focused in those areas. Some were unsure about – or reluctant to try – using other sites such as thigh or shoulder for needle siting, even when nodule formation was limiting the available infusion areas. In some cases it appeared that healthcare professionals who carried out needle changes were not adhering to best practice, for instance by

- siting needles too low in the abdomen or oriented vertically

- poor application of dressings so that needles were exposed or not held in place adequately
- poor hygiene
- insufficient site rotation

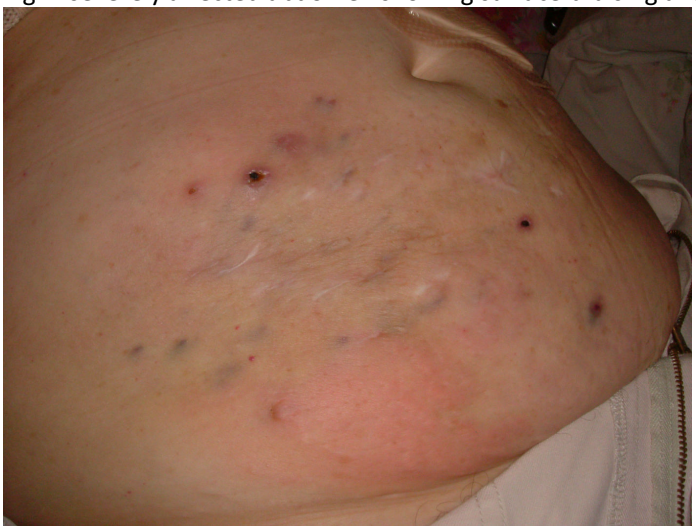
Observation during home visits indicated that self-administration was also not always satisfactory. Examples included poor hygiene, frequent casual re-siting of needles felt to be uncomfortable, removal of the needle by tugging the line sharply, and siting the needle in areas that were visibly inflamed. A shallow angle of needle insertion appeared to be a source of trauma, leading to greater irritation, staining of the skin and in one case was associated with necrosis and scarring of surface tissue.

Most participants had tried various prophylactics or remedies for nodule formation or associated tenderness. These included use of a hand-held electric massager, application of silicone gel patches or topical preparations (Sudocrem, E45 or other emollients, Fucidin and Emla) after removal of the needle. There were mixed views on the effectiveness of these measures. Massage and silicone patches were considered beneficial for tissue softening by those who used them, but participant descriptions suggested that the topical preparations were used for pain relief rather than for resolving nodules. Four people had received courses of ultrasound therapy previously and reported it helpful for resolving nodules. One person who had received a single session of US therapy did not find it beneficial.

Tissue assessment

Visual inspection and palpation revealed considerable variation in surface markings and tissue hardness. In some cases there was little evidence of deterioration; in others, blanched areas over hardened tissue, discoloration consistent with bruising or necrosis, broken skin and evidence of local infection was observed. Figure 1 provides a photographic example of observed surface changes.

Fig 1: severely affected abdomen showing surface bruising and scarring, erythema and necrosis.



Sonography of affected tissue revealed substantial departures from normal tissue appearance in many cases, including dermal thickening, irregularity and loss of definition of dermal-subdermal

boundary, and diffuse oedematous changes in the subcutaneous layer. Strong shadowing seen in one case may have been due to calcification or fibrotic changes. Palpable nodules varied in size between a few millimetres and several centimetres across. In some cases they had indistinct, lobulated forms. Figures 2 provides example of sonographic images of normal and affected tissue. A three-point scale describing and quantifying the extent of tissue changes was developed as a result of these observations, presented in table 3. A fuller account and discussion of the sonographic features identified has been published (Edwards et al., 2008).

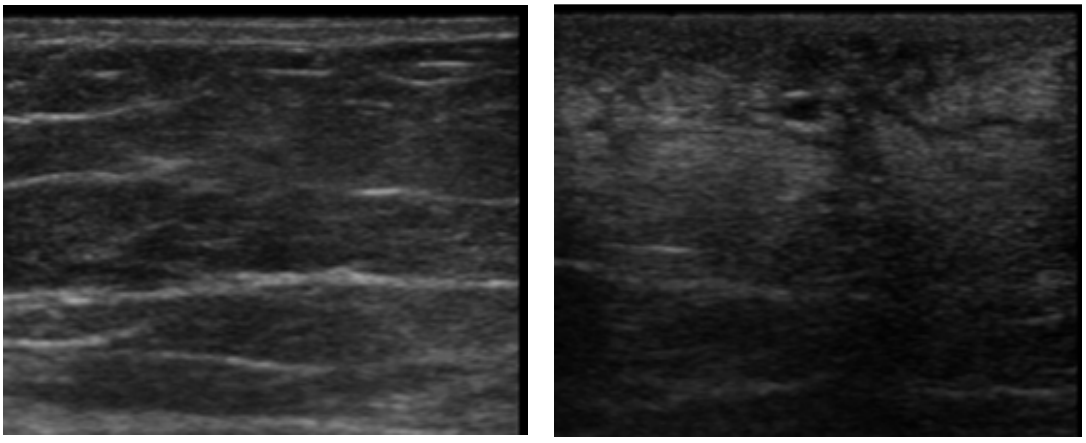
Table 3: Sonographic assessment of extent of tissue changes.

Severity	Sonographic features
1 mild	• Discernible focal hypoechoic or hyperechoic areas in Field of View (FOV) • Normal dermal thickness (typically 2mm) • Slight variations in dermal-subdermal boundary • Normal overall appearance of subdermis
2 moderate	• 1-2 focal hypoechoic or hyperechoic areas in FOV • Focal areas <1cm across • Slight thickening of dermis (typically 3-4mm) • Irregularity / some loss of definition in dermal-subdermal boundary • Limited diffuse changes in subdermis (loss of normal lobulated appearance of adipose tissue).
3 severe	• lobulated or >2 distinct focal hypoechoic or hyperechoic areas in FOV • Focal areas >1cm across • Significant thickening of dermis (>4mm) • Irregularity / substantial loss of definition in dermal-subdermal boundary • Substantial diffuse changes in subdermis (loss of normal lobulated appearance of adipose tissue. • Evidence of focal fibrosis or calcification

Scores assigned on the basis of overall appearance, all features not necessarily present in each case.

Fig 2: Sonographic images of abdominal tissue of a 61-year-old female, receiving apomorphine for 3 years. (a) normal abdominal subcutaneous tissue; (b) affected tissue. Depth 3cm, identical US settings for both images.

(a) (b)



Severity scores using the sonographic scale were assigned to each participant and non-parametric tests were used to check for associations between these scores and a variety of potential risk factors. SPSS 14 was used to calculate Kendall's tau and Spearman's rho, with significance set at p=0.05. No significant correlations were found between severity scores and time since diagnosis with PD, Hoehn and Yahr stage, age, body mass index, daily or hourly dose of apomorphine, hours

spent each day on infusion or reported history of allergic response. A moderate negative correlation was found, however, between severity score and number of years on apomorphine.

Table 4: Tests of correlation between sonography severity score and years on apomorphine

Test	Coefficient	P
Spearman's ρ	-0.46	0.03
Kendall's τ	-0.39	0.03

Several other trends were observed. Participants using the narrower gauge needle for infusion tended to have less severe tissue changes, and those siting their own needle (as opposed to having another person do it) tended to have more severe tissue changes. People with lean body frames often presented with smaller, well-defined nodules, whilst those with more adipose tissue at the infusion sites usually developed larger but more diffuse hardened areas. Both presentations could be problematic. Cases of poor needle-changing practice often coincided with significant deterioration in tissue appearance and quality, although not necessarily more profuse nodule formation.

Discussion

Nodule formation and associated tissue changes can present a considerable problem to people receiving infused apomorphine. Whilst nodules are thought to be reactions to the drug itself(Acland et al., 1998), other factors are likely to contribute to the severity of the tissue changes that have been described. Participant accounts and clinician observations suggest that infusion practices vary considerably, and departures from best practice may exacerbate reactions to the infusion.

The relatively small sample size may account for the fact that no statistically significant correlations were detected between most potential risk factors and sonography severity scores. Apomorphine dose is likely to be a risk factor because people receiving continuous infusions, rather than (lower dose) intermittent injections, tend to experience the most significant cutaneous reactions (Hughes et al., 1993, Deleu et al., 2004). In the clinic from which participants were recruited for this study, only patients receiving apomorphine by infusion were reported to have significant nodule formation. However the variation in severity observed in people on similar doses suggests that dose is not the only factor involved. The negative association between severity score and years on apomorphine appears counter-intuitive. It may also be that the longer people are receiving apomorphine, the more adept they become at preventing or treating nodule formation. Also, the severity score applies to sonography of only one area and does not take account of how extensively they are distributed. Nevertheless these findings support the contention that the severity of nodules depends on a variety of factors, not just apomorphine regime. Evaluating the contributions of potential risk factors, and interaction effects, would require a larger sample.

In the meantime, there may be scope for lessening nodule formation and other tissue reactions by attending to factors such as

- needle type
- needle-siting technique
- use of a wider area and rotation - not just alternation from side to side,
- improved hygiene
- prompt treatment of affected tissue.

Although guidelines for the use of apomorphine and management of nodules are available (Swinn et al., 2005, Todd and James, 2008), greater attention to the education of those receiving the drug, and of carers (family or health professionals) involved in infusion management, may be required.

Varying reports of the efficacy of different treatments suggest that sub-group analysis may help identify people more likely to respond to a particular treatment. The sonography severity scale developed in this study may be a useful measure for researchers to gauge the extent of tissue changes and the effectiveness of any treatments applied, but it remains to be validated. Caution is required in the use of sonographic images because their correspondence to tissue changes has not been verified by correlation with histology. Such studies are difficult as they may require large incisional biopsies (Requena, 2007). For the purposes of clinical assessment, palpation and observation may be more practical ways of monitoring nodule severity and deciding when further intervention is indicated.

For those experiencing nodules and other tissue reactions, hardening of the tissue was the biggest problem, primarily because it limits sites available for infusion. Clearly, where prophylaxis has not been successful, an effective treatment for these side effects is highly desirable. In addition to comments from participants in this study, our group has substantial anecdotal evidence from clinicians who have used therapeutic ultrasound, suggesting that it can be an effective treatment for apomorphine nodules. A pilot trial of the treatment by our group, reported elsewhere(Poltawski et al., In Press), was encouraging. Guidelines for ultrasound treatment based on our experience are available at http://www.electrotherapy.org/modalities/apomorphine.html. The possibility of portable therapeutic ultrasound units that can be used by patients at home is being investigated, since this would enable them to manage treatment independently. A combination of clean and careful needle-changing technique, deep tissue massage and therapeutic ultrasound may offer the best prevention and management plan for nodules.

The small sample size used in this study, and their recruitment from a single clinic, suggests that its findings may not be generalisable to the wider population. However, the demographic and clinical characteristics of the sample are similar to those reported in other studies (Hagell and Odin, 2001, Deleu et al., 2004, Katzenschlager et al., 2005).

Conclusion

This study has identified problems that are associated with the use of subcutaneous infusions of apomorphine hydrochloride. The severity of reaction appears to be affected by a numerous of factors, and better education of patients are carers regarding nodule prevention and management is recommended. Sonographic data are suggestive of broader structural changes in the tissue than has been previously reported. Palpation and sonography may be useful instruments for evaluation of tissue, and for monitoring effectiveness of treatment. Further studies to investigate factors associated with nodule evolution, and efficacy of different management strategies, are recommended.

Key points
Subcutaneous nodules are a common and potentially problematic side-effect of apomorphine infusion for Parkinson's Disease
Nodule severity may be affected by infusion-siting and needle-changing practices as much as by use

of the drug itself
Education of those responsible for administration of apomorphine infusions may be beneficial in reducing nodule formation
A range of treatments are available for nodules, and therapeutic ultrasound should be considered as part of a management strategy
Sonography may be a useful outcome measure in studies of nodule treatment effectiveness

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