Tolerability of intramuscular injections of testosterone ester in oil vehicle

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We undertook a prospective survey of the tolerability of deep i.m. injections of testosterone enanthate in a castor oil vehicle, the most widely used form of androgen replacement therapy. Over a period of 8 months, 26 men received 551 weekly injections into the gluteal, deltoid or thigh muscle and side-effects were recorded immediately and 1 week after each injection by the same nurse using a standardized questionnaire. Most injections caused no complaints [389/551, 70.6% (95% confidence interval 66.6–74.4%)] but minor local side-effects, mostly pain and bleeding, were common [162/551, 29.4% (25.6–33.4%)]; no serious side-effects were observed. Considering all side-effects, the gluteal site had fewer complaints and was less prone to bleeding but was painful more often than deltoid or thigh injection sites. The laterality of injection at any site had no significant effect on side-effects. The only systemic side-effect was episodes of sudden-onset, non-productive cough associated with faintness following eight injections [1.5% (0.6–2.9%)] which we speculate may have been due to pulmonary oil microembolism. We conclude that, when administered by an experienced nurse, deep i.m. injection of testosterone enanthate in a castor oil vehicle is generally safe and well tolerated but causes relatively frequent minor side-effects, including pain and bleeding. An improved depot form of testosterone would be highly desirable for androgen replacement therapy and hormonal male contraception.

Key words: androgen replacement therapy/intramuscular injection/laterality/side-effects/testosterone

Introduction

Testosterone has been used clinically in androgen replacement therapy for over 50 years (Nieschlag and Behre, 1990). Over the past few decades the most frequent mode of administering testosterone has been deep i.m. injections of testosterone esters in a vegetable oil vehicle. Despite this long usage, no systematic studies of side-effects from oil-based i.m. injections of testosterone esters could be located after extensive computer-based and manual library searching. The opportunity to study systematically the tolerability of these injections and the pattern of side-effects was provided by an ongoing male contraceptive study requiring healthy men to have weekly i.m. injections of testosterone enanthate in castor oil vehicle administered by the same research nurse for up to 18 months. The aims of this study were to estimate prospectively the pattern and incidence of side-effects of oil-based, deep i.m. injections in normal men and to determine whether anatomical site and/or laterality of injection influences the incidence of these side-effects.

Materials and methods

Study design

This was a prospective survey of adverse effects from i.m. injections of oil-based testosterone enanthate. The injections were given during a World Health Organization (WHO) contraceptive efficacy study of a prototype hormonal male contraceptive and the design and results of that study have been described in detail elsewhere (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Injections were given and side-effects recorded by the same right-handed research nurse (M.A.M.) both immediately following and 1 week after injection using a standard questionnaire. The questionnaire recorded date, site and side of injection as well as eliciting specific responses to potential side-effects, including pain or stinging, bleeding or bruising, swelling, numbness, muscle twitch, erythema, faintness, coughing. For reported symptoms, the duration, severity and degree of interference with daily living was recorded. For the analysis, the categories of pain and bleeding included both immediate and delayed reports. The criterion for recognition of pain was the subject's response to the question 'Was that injection painful?' and was applied and recorded consistently for each subject.

Subjects and injections

Men involved in this study were 26 healthy males aged between 21 and 45 years recruited from the general population to participate in a multicentre male contraceptive study (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Entry criteria were that men had to be healthy, in a stable relationship and requiring contraception. Volunteers were required to have their injection administered by the study nurse (M.A.M.) on the same day (± 1 day) each week for up to 18 months. The vials of testosterone enanthate (250 mg in

1 ml castor oil, Testoviron Depot; Schering AG, Berlin, Germany) were kept at air-conditioned room temperature and injections of 200 mg (0.8 ml) were administered with a 21 gauge (0.80×38 mm) needle into one of three muscular sites: the anatomical site of the injection (gluteal, deltoid, thigh) was chosen by the subjects and injections were routinely alternated from side to side. Deep i.m. injections were given according to standard methods, including aspirating the syringe to exclude vascular puncture before injection and injecting slowly.

Data analysis

Data were cross-tabulated and analysed by appropriate methods for categorical data using BMDP software (BMDP Statistical Software Inc., Los Angeles, CA, USA) implemented on a VAX computer network. Power was estimated using Poisson confidence intervals (Gardner and Altman, 1989) and PASS software (Hintze, 1991).

Results

During 8 months, 602 scheduled injections were given without any injections missed and complete information was available after 551 (92%) injections. The remainder were accounted for by injections administered when men were out of Sydney for work or holidays. During this period, only two out of 26 men changed their preferred site of injection.

Most injections caused no complaints [389/551, 70.6% (95% confidence interval, 66.6–74.4%)] and any adverse effects were recorded after only 162/551 [29.4% (25.6–33.4%)] injections. There were no significant differences in rate of complaints of side-effects according to laterality of injection for gluteal [left 19/68 (27.9%) versus right 27/151 (17.9%)], thigh [left 17/51 (33.3%) versus right 27/85 (31.8%)] and deltoid [left 49/114 (43.0%) versus right 29/82 (35.4%)]. The overall pooled (Mantel–Haenszel) relative risk was 1.40 [95% (confidence interval 0.95–2.06), test for homogeneity of risk across strata $P = 0.61$].

Considering all adverse effects (Table I), the total number of complaints was significantly higher for deltoid [2.0 (1.5–2.8)] and thigh [1.6 (1.1–2.3)] than for gluteal sites of injection. Considering specific adverse effects, gluteal injections caused more complaints of pain [relative risk 2.4 (1.3–4.3)] and fewer of bleeding [0.16 (0.08–0.32)] compared with the other two sites combined (Table I). Immediate bleeding was minor in all cases, requiring only light topical pressure for a few minutes or was recorded in retrospect as minor bloodspot staining of clothing or slight bruising. Pain was usually not sufficient to require analgesia; at worst, discomfort was present for several days on sitting or lying on the injection site. There were no reports of local erythema or acute inflammatory reactions following injections. Apart from coughing episodes, all reported reactions were considered by volunteers and investigators as minor; none ceased injections due to such side-effects during the study.

Table I. Side-effects of i.m. injections

Side-effect	Deltoid	Thigh	Gluteal	Total	*P*
Nil	119 (61%)	94 (69%)	176 (80%)	389 (70.6%)	<0.001
Bleeding	49 (25%)	27 (20%)	8 (4%)	84 (15.3%)	<0.001
Pain	13 (7%)	5 (4%)	23 (11%)	41 (7.4%)	0.050
Muscle twitch	10 (5%)	5 (4%)	7 (3%)	22 (4%)	0.598
Cough ± faint	4 (2%)	3 (2%)	2 (1%)	9 (1.6%)	0.552
Other	1 (1%)	2 (1%)	3 (1%)	6 (1.1%)	0.621
Total	196 (100%)	36 (100%)	219 (100%)	551 (100%)	

The only systemic side-effect was coughing fits observed immediately after eight injections [prevalence 1.5% (0.6–2.9%)], associated with faintness and sweating on one occasion. On another occasion, faintness and sweating occurred without coughing. Two characteristic cases are described. In the first, a 25 year old man without known asthma or allergies developed an intense, non-productive cough without wheeze immediately after having received 21 previous i.m. injections into the gluteal muscle uneventfully. He also developed an injection site reaction after withdrawal of the injection needle which required him to remain recumbent until the coughing subsided (5 min). After this episode he had six further weekly injections without recurrence or complaint before he discontinued from the study to initiate a planned pregnancy. In the second, a 35 year old man without known asthma or allergies and having received 24 injections into the deltoid muscle, including one previous similar episode, developed an intense non-productive cough with associated pallor, nausea and chest tightness but no wheeze or injection site reaction which gradually subsided after 10 min. He subsequently had another 35 injections into the gluteal muscle without experiencing further such episodes.

The power of this study was >50, >80 and >90% to detect (one-sided, $\alpha = 0.05$) events with underlying prevalence of 1.3, 1.7 and 2.0% respectively. Conversely in order to detect events with a prevalence of 1.0% with 80% power, a sample size of 4000 observations would have been required. For adverse effects not observed in this study, the upper 95% (Poisson) confidence limit was 0.67%.

Discussion

Depot formulations are widely used to enhance therapeutic compliance and convenience by prolonging the duration of drug action. Among the most widely used depot formulations are drug esters administered in an oil vehicle. Esterification of base drugs with appropriate lipophilic fatty acids forms a pro-drug ester whose hydrophobic side-chains partition preferentially into the oil vehicle. Prolongation of pro-drug release is provided by the rate-limiting retarded diffusion of the pro-drug ester into the extracellular fluid where ubiquitous non-specific esterases hydrolyse the ester bond to liberate active drug. In addition to forming a hydrophobic depot, the oil vehicle limits local chemical irritation and cytotoxicity caused by some drugs (Svendsen and Blom, 1984). This oil-based formulation has been widely and successfully used for sex steroids including androgens, oestrogens and progestins as well as psychotrophic drugs such as fluphenazine, haloperidol and related major tranquilizers (Gilman *et al.*, 1990). Oils derived from vegetable sources such as castor or sesame seeds

or peanuts (*Arachis*) have been widely used whereas mineral oils are too irritating (Symmers, 1955).

Testosterone esters in an oil vehicle have been for decades the most widely used modality of delivering androgen replacement therapy in male hypogonadism (Behre *et al.*, 1990). Despite this long usage, or perhaps because of it, there have been few systematic studies of tolerability of i.m. administration of testosterone esters in oil-based formulations. The general pharmacology of i.m. injections has been reviewed (Schou, 1971; Greenblatt and Koch-Weser, 1976; Zuidema *et al.*, 1988) but most studies concern aqueous formulations of drugs administered to hospitalized patients. For example, the only large survey of i.m. injections reported adverse local effects in only 0.4% of 12 134 hospitalized patients receiving i.m. injections of drugs in aqueous formulations (Greenblatt and Allen, 1978). No comparable surveys in ambulatory care settings or involving oil-based steroid ester formulations are available to our knowledge.

Overall, while nearly 30% of our subjects had some complaints, they were considered by patients and investigators as minor in nature and serious adverse effects were not observed. Satisfaction was greatest for the gluteal site, lowest for the deltoid, with the thigh being intermediate. Discrepancies in patterns of pain and bleeding accounted for these differences. The level of recorded complaints may be conservative as determined among highly motivated volunteers agreeing to participate in a prolonged study requiring weekly i.m. injection for up to 18 months. Administration by less expert staff or by self-injection may lead more frequently to dissatisfaction. Furthermore, the tolerance of discomfort among hypogonadal men requiring life-long androgen replacement therapy or fertile men considering hormonal male contraception among other family planning methods may be lower. Although the sites of injection were not randomized but were selected by the subjects, it is unlikely that this significantly biased the outcomes, unless men predisposed to complain of side-effects were systematically more likely to choose a particular injection site, which seems unlikely. Although this survey included nearly 550 injections, it could provide reliable estimates for only relatively common (>2%) side-effects. The frequency of rare side-effects, especially those not observed during the survey period, could not be reliably estimated. For example, the power of this survey was adequate (>80%) for events with a true underlying rate of occurrence of $\geqslant$1.7%, but would need to include more than seven times as many injections to detect events with a 1.0% prevalence.

The lower risk of minor bleeding at the gluteal injection site may be attributed to its lower blood flow (Evans *et al.*, 1975) as well as the fact that most gluteal i.m. injections are actually intralipomatous (Cockshott *et al.*, 1982) and adipose tissue blood flow is even lower than muscle. Conversely, the reason for the higher rate of discomfort following gluteal injections is unclear and conflicts with experimental observations that intralipomatous injection causes less local toxicity than i.m. injection of irritant psychoactive drugs in rabbits (Svendsen *et al.*, 1985). The precise cause of injection pain remains unclear (Travell, 1955), although presumably local cytotoxicity due to insertion of the injection needle as well as the chemical nature of the drug, its vehicle and their local metabolites are relevant factors. Possibly the functional significance of various anatomical sites may also influence injection pain. For example, extrinsic pressure on the injection site may be more common after gluteal injections (e.g. during sleeping or sitting) than for other sites.

More serious local injection site side-effects, including sciatic nerve damage, muscular fibrosis, gas gangrene, and distal ischaemia following intra-arterial injection were not observed in this survey, consistent with their rarity among adults. We also observed no evidence of either acute or chronic inflammatory reactions which have been reported rarely to cause lipogranulomas and/or pseudotumour foreign body reactions (Symmers, 1955; Balogh, 1986; Hamann *et al.*, 1990; Khankhanian and Hammers, 1992) causing diagnostic confusion and serious clinical consequences. As inflammatory reactions have been reported following subdermal injections of vegetable oils alone (Brown *et al.*, 1944) or containing non-steroidal drug esters (Hamann *et al.*, 1990) while aqueous suspensions of testosterone esters are non-irritating (Behre and Nieschlag, 1992), the side-effects observed in this study are most likely to be attributable to the oil vehicle rather than the testosterone ester. As the present survey had sufficient power to exclude non-observed events with an underlying frequency of at least 2%, this figure provides an upper limit for the likelihood of such reactions which were not observed during our study.

The only systemic side-effect observed was coughing reactions consisting of sudden-onset, non-productive coughing with or without faintness which was observed on eight occasions giving a prevalence of 1.5% [95% (confidence interval 0.6–2.9%)]. Although disturbing to subjects, the coughing was transient, lasting for 10 min at most and subsided spontaneously without known sequelae. Acute drug-related respiratory distress not due to bronchospasm or laryngopulmonary oedema is rare but has been described after i.m. administration of an oil-based solution of pitressin tannate (Hoigne *et al.*, 1990). The sudden onset of coughing without wheeze or injection site reaction together with a history of uneventful injections before and after the episodes suggests an idiosyncratic, mechanical phenomenon related to a particular injection. Neither allergy to testosterone enanthate or the castor oil vehicle have been reported and would seem clinically unlikely given the isolated occurrence of the events and speed of onset. We speculate that these respiratory reactions may be due to pulmonary oil microembolization following lymphogenic (Svendsen *et al.*, 1980) or venous absorption of oil (Svendsen and Aaes-Jorgensen, 1979), leading to transient acute pulmonary hypertension possibly related to mechanical vascular occlusion and/or intravascular liberation of free fatty acids from hydrolysis of the oil (Hofmann *et al.*, 1976; Szabo *et al.*, 1977). Clinically significant pulmonary manifestations of oil embolism have been reported following injection of 2.5 ml oil reaching the bloodstream (Bron *et al.*, 1963; Gough and Thomas, 1964). The relatively mild clinical manifestations observed with our smaller injection volume (0.8 ml) are consistent with this mechanism. An alternative, albeit unlikely, explanation that cannot be fully excluded is that intralipomatous injection

may rarely provoke embolism of cellular fragments such as adipocyte lipids. The low frequency and mild clinical features observed do not require any major change in current standard clinical practice but suggest caution when injecting larger volumes of oil i.m. Apart from the recent addition of warnings concerning the occurrence of 'coughing fits, urge to cough and respiratory distress' to the product information for testosterone enanthate, such side-effects do not appear to have been reported previously.

We conclude that deep i.m. injections of testosterone enanthate in castor oil vehicle are generally safe and reasonably tolerated when administered by a single experienced research nurse. Minor side-effects, mainly pain and bleeding, are relatively common but serious side-effects are rare. The anatomical site, but not laterality, of injections influences tolerance, as the gluteal site has fewer overall side-effects and is less prone to bleeding but more liable to pain than the deltoid or thigh sites. Coughing reactions, not previously reported but observed after 1.5% of injections, we speculate may be due to pulmonary oil microembolization. As our observations reflect the properties of an oil vehicle, similar findings would be expected with other similarly formulated drugs. These findings highlight the need for better depot testosterone formulations for patients requiring life-long androgen replacement therapy, as well as for future regimens for hormonal male contraception.

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References

Balogh, K. (1986) The histologic appearance of corticosteroid injection sites. *Arch. Pathol. Lab. Med.*, **110,** 1168–1172.

Behre, H.M. and Nieschlag, E. (1992) Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. *J. Clin. Endocrinol. Metab.*, **75,** 1204–1210.

Behre, H.M., Oberpenning, F. and Nieschlag, E. (1990) Comparative pharmacokinetics of androgen preparations: application of computer analysis and simulation. In Nieschlag, E. and Behre, H.M. (eds), *Testosterone: Action Deficiency Substitution.* Springer-Verlag, Berlin, pp. 115–135.

Bron, K.N., Baum, S. and Abrams, H.L. (1963) Oil embolism in lymphography. Incidence, manifestations, and mechanisms. *Radiology,* **80,** 194–202.

Brown, W., Wilder, V. and Schwartz, P. (1944) A study of oils used for intramuscular injections. *J. Lab. Clin. Med.*, **29,** 259–264.

Cockshott, W.P., Thompson, G.T., Howlett, L.J. and Seeley, E.T. (1982) Intramuscular or intralipomatous injections? *N. Engl. J. Med.*, **307,** 356–358.

Evans, E.F., Proctor, J.D., Fratkin, M.J., Velandia, J. and Wasserman, A.J. (1975) Blood flow in muscle groups and drug absorption. *Clin. Pharm. Ther.*, **17,** 44–47.

Gardner, M.J. and Altman, D.G. (eds) (1989) *Statistics with Confidence: Confidence Intervals and Statistical Guidelines.* British Medical Journal, London.

Gilman, A.G., Rall, T.W., Nies, A.S. and Taylor, P. (eds) (1990) *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* Pergamon Press, New York.

Gough, J.H. and Thomas, M.L. (1964) Pulmonary complications following lymphography. *Br. J. Radiol.*, **37,** 416–421.

Greenblatt, D.J. and Allen, M.D. (1978) Intramuscular injection-site complications. *J. Am. Med. Assoc.*, **240,** 542–544.

Greenblatt, D.J. and Koch-Weser, J. (1976) Intramuscular injection of drugs. *N. Engl. J. Med.*, **295,** 542–546.

Hamann, G.L., Egan, T.M., Wells, B.G. and Grimmig, J.E. (1990) Injection site reactions after intramuscular administration of haloperidol decanoate 100 mg/ml. *J. Clin. Psychiatry,* **51,** 502–504.

Hintze, J.L. (1991) *NCSS: Power Analysis and Sample Size version 1.0.* Published by J. L. Hintze, Kaysville, USA, pp. 143–149.

Hofmann, K., Brunner, P. and Tulusan, A.H. (1976) Abbau oliger substanzen in der kaninchenlunge. *Virchows Arch., Abt. A, Path., Anat. Histol.*, **369,** 347–358.

Hoigne, R., Jaeger, M.D., Hess, T., Wymann, R., Muller, U., Galeazzi, R., Maibach, R. and Kunzi, U.P. (1990) Acute severe dyspnea as a side effect of drugs. Report from the CHDM (Comprehensive Hospital Drug Monitoring). *Schweiz. Med. Wochenschr.,* **120,** 1211–1216.

Khankhanian, N.K. and Hammers, Y.A. (1992) Exuberant local tissue reaction to intramuscular injection of nandrolone decanoate (Deca-Durabolin) – a steroid compound in sesame seed oil base – mimicking soft tissue malignant tumors: a case report and review of the literature. *Mil. Med.*, **157,** 670–674.

Nieschlag, E. and Behre, H.M. (eds) (1990) *Testosterone: Action Deficiency Substitution.* Springer-Verlag, Berlin.

Schou, J. (1971) Subcutaneous and intramuscular injection of drugs. In Brodie, B.B., Gillette, J.R. and Ackerman, H.S. (eds), *Concepts in Biochemical Pharmacology.* Springer-Verlag, Berlin, pp. 47–66.

Svendsen, O. and Aaes-Jorgensen, T. (1979) Studies on the fate of vegetable oil after intramuscular injection into experimental animals. *Acta Pharmacol. Toxicol.*, **45,** 352–378.

Svendsen, O. and Blom, L. (1984) Intramuscular injection and muscle damage: effects of concentration, volume, injection speed and vehicle. *Arch. Toxicol.*, Suppl. **7,** 472–475.

Svendsen, O., Dencker, S.J., Fog, R., Gravem, A.O. and Kristansen, P. (1980) Microscopic evidence of lymphogenic absorption of oil in humans receiving neuroleptic oily depot preparations intramuscularly. *Acta Pharmacol. Toxicol.*, **47,** 157.

Svendsen, O., Blom, L., Aaes-Jorgensen, T. and Larsen, J.J. (1985) Local toxicity of different drugs after intramuscular or intralipomatous injection in pigs: serum concentrations after three different formulations of cis(Z)-clopenthixol. *Acta Pharmacol. Toxicol.*, **57,** 78–87.

Symmers, W. (1955) Simulation of cancer by oil granuloma of therapeutic origin. *Br. Med. J.*, **2,** 1536–1539.

Szabo, G., Magyar, Z. and Reffy, A. (1977) The role of free fatty acids in pulmonary fat embolism. *Inj., Br. J. Accident Surg.*, **8,** 278–283.

Travell, J. (1955) Factors affecting pain of injection. *J. Am. Med. Assoc.*, **158,** 368–371.

WHO Task Force on Methods for the Regulation of Male Fertility (1990) Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet,* **336,** 955–959.

Zuidema, J., Pieters, F.A.J.M. and Duchateau, G.S.M.J.E. (1988) Release and absorption rate aspects of intramuscularly injected pharmaceuticals. *Int. J. Pharmaceutics,* **47,** 1–12.

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