

# Complications of injectable testosterone undecanoate in routine clinical practice

T Middleton, L Turner, C Fennell, S Savkovic, V Jayadev, A J Conway and D J Handelsman

Andrology Department, ANZAC Research Institute, Concord Hospital, University of Sydney, Sydney, New South Wales 2139, Australia

Correspondence should be addressed to D J Handelsman  
**Email**  
djh@anzac.edu.au

## Abstract

**Objective:** Injectable testosterone undecanoate (TU) was marketed within the last decade, but its complications in routine clinical practice are not well defined.

**Design and methods:** Prospective observational study of consecutive TU injections in an Andrology Clinic to estimate the incidence of i) immediate cough/syncope due to pulmonary oil microembolisation (POME), ii) post-injection haematoma and iii) the prevalence of secondary polycythaemia.

**Results:** In 3022 injections given to 347 patients over 3.5 years, POME was observed after 56 injections (66% mild, 19% severe; 40% with onset before injection completed) in 43 patients. The incidence of 19 (95% CI 14–24) per 1000 injections did not differ between three experienced nurse injectors, but recurrences were more frequent than by chance. No post-injection haematoma was reported including after 269 injections to men taking antiplatelet, anticoagulant or both drugs (upper 95% confidence limit 1%) with 56 not withholding drugs prior to TU administration (upper 95% confidence limit 5.4%).

Mean haematocrit was  $0.44 \pm 0.04$  (s.d.) with 25 (7%)  $> 0.50$ , 14 (4%)  $> 0.52$  and 3 (1%)  $> 0.54$ .

**Conclusion:** TU injections produce a low incidence of POME with injections by experienced nurses, but recurrence is more frequent than by chance. Post-injection haematoma was not observed even among men using anticoagulant and/or antiplatelet drugs, and polycythaemia was a minor problem rarely requiring treatment other than optimising inter-injection interval.

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## Introduction

Testosterone has been in clinical use for over 75 years (1) in a wide variety of products (2). Since the mid-1950s, injectable testosterone esters in oil vehicle (3) has been the most widely used testosterone formulation for its affordability and its depot properties which ease compliance by wide inter-injection spacing. Testosterone undecanoate (TU), available for decades in an oil-filled oral capsule marketed world-wide (other than the USA) (4, 5), was first developed as an injectable oil vehicle-based formulation in China in the 1980s (6) and subsequently reformulated for marketing in Europe in 2003 and subsequently worldwide over the last decade (7). Within that decade, TU has become one of the two most commonly prescribed testosterone products in Australia (8) and other countries (9).

Testosterone replacement therapy for male hypogonadism due to pathological disorders of the reproductive system aims to restore the lifetime health outcomes of eugonadal men. While all testosterone products can provide effective testosterone replacement therapy, the choice of formulation is primarily determined by patient convenience and physician familiarity, aiming to assure long-term compliance with lifelong treatment (2). Similarly, while reviews of testosterone treatment focus mostly on efficacy rather than safety (10), generically, testosterone replacement therapy has a good safety record (11) while each product has specific side-effects mostly related to their mode of administration. For injectable testosterone esters in an oil vehicle, the most relevant are injection site pain (12) or haematoma, pulmonary oil

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microembolism (POME) (13, 14) and secondary polycythaemia (15). Most studies of testosterone's safety profile originate from clinical trials primarily designed to meet the requirements of regulatory authorities to enable a product to be marketed. It is common experience that post-marketing safety profile may differ from the clinical development program that achieves marketing approval with key differences arising for reasons including detection of rare and previously unrecognised events, confounding by between-centres differences in clinical practice, commercial motivations of sponsors and the artificial framework of clinical registration trials. We have therefore undertaken a prospective surveillance study of TU injections in the routine clinical practice in an experienced single academic centre outside a research setting with a focus on POME, haematoma and polycythaemia.

## Subjects and methods

### Study design

This study was a prospective survey of patients attending the Andrology Department of Concord Hospital to receive TU injections between July 2010 and March 2014 for androgen deficiency due to pathological disorders of the hypothalamo–pituitary–testicular axis. Blood was sampled for serum testosterone monitoring before testosterone injection. Testosterone injections were administered by the clinical staff of the Andrology Department according to the standard protocol by slowly administering deep i.m. injection into the upper outer quadrant of the buttock after aspiration to exclude venous injection. At the time of each injection, clinical staff recorded demographic details and observations for POME episodes between start of injection and leaving the clinic. POME was considered to be present when an unexpected, non-productive cough occurred during or immediately after (within minutes) TU injection. The coughing episode occurred with or without a sensation of flushing, faintness or anxiety and was not due to a chronic cough, acute asthma or an upper respiratory tract infection. Symptoms usually took a few (up to 10) minutes to resolve.

The departmental policy, on haematology advice, was to temporarily interrupt anticoagulants or antiplatelet medication before deep i.m. injections to prevent haematoma, subject to safety review by the doctor prescribing the anticoagulant or antiplatelet drug. In this study, men receiving antiplatelet and/or anticoagulant medications were asked whether they had stopped their medication and, if so, for how long, as well as whether they

experienced a haematoma following their previous TU injection.

Patients were routinely monitored for polycythaemia by full blood counts at least once per year for men over the age of 50 years, as well as by cross-sectional campaign surveillance for the stable population of all men attending for regular testosterone replacement therapy.

### Subjects and injections

The participants involved in this study were patients of the Andrology Department aged between 20 and 75 years, who were receiving testosterone replacement therapy for a variety of pathological disorders of the hypothalamic, pituitary or testis (but not andropause) or were female-to-male transgender patients. Injections were administered by experienced nurses delivering deep i.m. injections of 1000 mg of TU in 4 ml of castor oil vehicle using a 21-gauge needle. Injections were administered deeply into the right and left gluteal muscle (on an alternating basis) slowly over a period of 2 min. The patients were observed until they left the clinic, in most cases within a few minutes of receiving their injection. When patients experienced POME symptoms, they were observed until the symptoms resolved, usually within 10 min of the onset.

### Assays

Haematocrit was measured by standard autoanalyser methods and serum testosterone by immunoassay.

### Statistical analysis

Data were analysed by appropriate methods for continuous or categorical data using NCSS version 9 and StatXact version 9 software.

## Results

During the 3.5 years of this survey, 3022 TU injections were administered to a total of 347 patients, whose androgen deficiency causes are given in Table 1.

### Cough/syncope episodes

There were a total of 56 POME episodes observed in 43 patients, associated with TU giving an overall incidence of 19/1000 injections (95% CI 14–24 per 1000 injections). One patient experienced a POME episode during his first i.m. TU injection and the remainder had received between

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**Table 1** Causes of androgen deficiency.

Cause of androgen deficiency	Number
Primary hypogonadism <sup>a</sup>	144
Secondary hypogonadism <sup>b</sup>	89
F2M transgender	96
Other	18
Total	347

<sup>a</sup>Klinefelter's syndrome, orchidectomy, cryptorchidism, testicular agenesis, trauma, infection, torsion or cytotoxic/irradiation damage.

<sup>b</sup>Kallmann's syndrome, IHH, pituitary or cerebral tumour, delayed puberty.

one and 30 TU injections (median 17 previous asymptomatic injections, inter-quartile range (IQR) 17) before their observed POME episode in this study.

POME episodes were experienced by patients due to a wide variety of underlying clinical conditions comprising Klinefelter's syndrome (8, 19%), idiopathic hypogonadotrophic hypogonadism including Kallmann's syndrome (7, 16%), hypogonadism following castration (4, 9%), pituitary tumour/surgery (4, 9%), chemotherapy (6, 14%), other (testicular pathology, male contraception 5, 12%) or F2M transgender (9, 21%). These patients were aged between 22 and 74 years (26% aged <35 years, 42% aged 36–50 years, 19% aged 51–65 years and 12% aged 66 years and over) and had BMIs ranging from 15.2 to 38.3 kg/m<sup>2</sup> (median 25.7 kg/m<sup>2</sup>; IQR 4.95 kg/m<sup>2</sup>). There was no significant difference between men who had a POME episode in the time since last injection and in serum testosterone immediately before the index injection (Table 2).

Onset of symptoms was during injection for 40% and duration of coughing (documented for 51/56 episodes) ranged between 1 and 10 min (median duration 3 min; IQR 3 min). Severity of symptoms (documented 53/56) was recorded as very mild or mild (66%), moderate (15%) or severe (19%). All episodes were managed conservatively within the clinic and supplementary oxygen was never required.

There was no significant difference between the rates of POME episodes observed between three experienced nurse injectors who administered 98% (2973) of all injections (Table 3). The risk of recurrent episodes of cough/syncope (Table 4) was significantly greater than that expected by chance ( $P=0.034$ , extended Fisher's test) deviating from a Poisson distribution (mean and variance=0.12).

### Haematoma

Among the 3022 injections, 269 (prevalence 8.9%) were administered to patients using prescribed antiplatelet (aspirin  $n=225$ ; asasantin  $n=3$ ; clopidogrel  $n=15$ ;

clopidogrel/aspirin  $n=1$ ) or anticoagulant (warfarin  $n=25$ ; enoxaparin  $n=2$ ) therapy with two patients on both clopidogrel and warfarin. Although the clinic's routine practice based on haematological advice was for patients to temporarily interrupt antiplatelet/anticoagulant therapy before the TU injection, this was subject to the medical indication and judgement of the patient's doctor prescribing the antiplatelet/anticoagulant medication. Most patients did interrupt antiplatelet/anticoagulant treatment for a median of 7 days (aspirin median 7, 1–28 days; clopidogrel median 4.5 days, 2–11 days; clexane median 4.5 days, 3–6 days; warfarin median 4 days, 2–94 days). For 56 injections, the antiplatelet/anticoagulant medication was not interrupted. There were no patient reports of significant haematoma post-TU injection during this study period, giving an upper 95% confidence limit for significant haematoma of 0.1% for the whole population of men receiving TU injections, of 1.0% for men prescribed anticoagulant/antiplatelet medication and 5.4% for men who did not interrupt antiplatelet/anticoagulant medication.

### Polycythaemia

Haematocrit measurement was available for 347 patients (with between one and 23 measurements available for each patient). Using the first measurement, the haematocrit was 0.44 (0.002 s.d.; quartiles 0.42, 0.44, 0.47; range 0.31–0.56) with 25 (7.2%) >0.50, 14 (4.0%) >0.52 and 3 (0.9%) >0.54.

### Discussion

Injectable TU has been marketed for over 10 years and is now one of the most commonly prescribed products for testosterone replacement therapy (8, 9). While the safety profile under clinical trial conditions is well established

**Table 2** Inter-injection interval and trough serum testosterone.

	Cough	No cough
Number of injections	55	2750
Time since previous injection (days)		
Mean $\pm$ s.e.m.	87 $\pm$ 7	89 $\pm$ 1
Median (quartiles)	84 (70, 86)	84 (70, 90)
Serum testosterone (nmol/l)		
Mean $\pm$ s.e.m.	16.2 $\pm$ 1.1	15.9 $\pm$ 0.1
Median (quartiles)	13.7 (11.5, 21.0)	14.8 (11.3, 19.4)

No difference between injections with or without cough (all  $P$  values >0.70).

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**Table 3** Number and rate per injection of cough/syncope episodes according to experienced nurse injectors.

Nurse	Number of injections	Cough/syncope episodes	Rate of cough/syncope (per 100 injections)
1	1286	27	2.1
2	714	10	1.4
3	973	20	2.1

(16, 17, 18, 19, 20, 21), its complications in routine clinical practice outside clinical trials have been less clearly established.

This study provides the most detailed characterisation of the clinical features of POME since its original description in men having deep gluteal i.m. injections of 0.8 ml testosterone enanthate in castor oil vehicle (13). This was subsequently confirmed in a Chinese study involving regular gluteal i.m. injections of 500 mg TU in 4 ml mellaleuca (mistranslated as 'tea seed') oil (14). In this study, POME has a rapid onset, usually during injection or shortly thereafter, lasting <10 min (median 3 min) and mostly mild in severity with no lasting sequelae. Its occurrence seems unrelated to age, underlying cause of hypogonadism or experienced nurses administering injections. The study design precluded evaluating the impact on POME incidence of less experienced nurses or doctors. It may also underestimate the occurrence of POME episodes that occurred after the patients left the clinic; however, based on our experience we believe this is rare if it ever occurs. The incidence in this study of 19/1000 injections is close to the rate originally described of 15 (95% CL 6–29) per 1000 injections (13) where both used castor oil vehicle, although with more different volumes (4 vs 0.8 ml) per injection. These estimates are however very different from the much lower incidence of POME reported to the FDA during the clinical development (1.5 cases/10 000 injections) and during post-marketing surveillance (0.7 cases/10 000 injections) in the US registration clinical trials of injectable TU (750 mg in 3 ml castor oil) (22). This major apparent discrepancy may be due to the manner of recording POME in the US clinical trials, which were marked by the incidence of POME being a significant hurdle to FDA registration. In addition to reducing the injection volume from 4 to 3 ml, the sponsor of the clinical trials employed two independent adjudicators, both former FDA employees without clinical experience of testosterone injections, who created an ad hoc case definition of POME after the conclusion of the trials.

The essential major criterion was paroxysmal cough with undue emphasis on the paroxysmal pattern. Using this case definition and written reports from centres, they discounted 97% (107 of 110 reports in 102 men) of putative POME reports with 23 regarded as 'intermediate' and 84 as not POME. No specific definition of 'intermediate' cases was provided, but if the 'intermediate' cases were included the rate of POME is comparable with our findings (13 vs 19/1000 injections). Systematic under-reporting of adverse cardiovascular effects of testosterone has been reported in commercially sponsored clinical trials (23).

The mechanism of POME appears to involve inadvertent entry of injected oil vehicle into the venous circulation with subsequent transfer to the pulmonary microvasculature. The basis for this interpretation arises from experimental animal studies showing pulmonary embolism in dogs and rabbits following i.m. injection of vegetable oils (24). There is also corroborative clinical evidence of lymphogenic absorption in humans after oil vehicle depot injections (25) as well as following accidental introduction of oil-based radiocontrast into the bloodstream during myelography, which produced cough and radiographic visualisation of contrast in the lungs (26, 27, 28). This non-thrombotic mechanism of POME should not be confused with the numerous prothrombotic genetic thrombophilias, such as Factor V Leiden (29). These features suggest that POME would be a random event, an interpretation supported by the lack of influence of age, underlying disease or between-injector differences among experienced nurses; however, the non-random risk of recurrence suggests that additional factors such as anatomical differences between individuals or of expectation by non-blinded reporters may be involved. Interestingly, confirming the higher than expected rate of POME recurrence, in the reported US clinical trials, eight of 102 men (8%) experienced a second episode of POME and one of ten men (10%) with 'intermediate' POME

**Table 4** Frequency of cough/syncope episodes and recurrences.

Number of cough/syncope episodes per patient	Number of patients	Expected number <sup>a</sup>
0	305	306
1	30	37
2	10	2
3	2	0

<sup>a</sup>According to Poisson distribution with mean and variance=0.12.

experienced a recurrence, both of which greatly exceeded the study's reported overall incidence of POME (22).

One potential adverse effect of deep i.m. injections of a large volume of oil vehicle is the risk of injection-induced haematoma. This risk is greatest among men with a bleeding disorders or using anticoagulant or antiplatelet medication indicated by incidental co-morbidities, and has led to recommendations that i.m. injections should not be given to men taking anticoagulants (30, 31). Nevertheless, previous small studies have shown that i.m. injection in an aqueous vehicle can be administered safely to patients receiving anticoagulant medications without increased risk of local bleeding (32, 33, 34, 35, 36); however, the use of larger volume of oil vehicle may change such risks. This study, based on self-report, did not record any instance of post-injection haematoma, allowing us to establish plausible upper 95% confidence limits on the risk of post-injection haematoma as 0.1% for all men having TU injections, 1% for men using anticoagulant or antiplatelet medication but who interrupt that medication temporarily for the TU injection and 5.4% for men continuing to use such medication at the time of TU injection. These findings are reassuring that such post-injection haematoma is a relatively low risk for men having TU injection, including those taking antiplatelet or anticoagulant medication. The present findings are consistent with the pooled European and US clinical registration studies for 750 and 1000 mg TU injections in 3 and 4 ml castor oil vehicle, respectively, where there were only two reports of injection site haematoma/haemorrhage among 725 patients (22); whether these men were using anticoagulant or antiplatelet medications is not reported.

Testosterone has prominent dose-dependent stimulatory effect on erythropoiesis, involving stimulation of erythropoietin, suppression of hepcidin and increased iron incorporation into erythrocytes (37, 38, 39, 40). Consequently, testosterone replacement therapy can result in polycythaemia (11, 41), which is more prominent among older men (42) and those having injectable or implantable rather than oral testosterone (15). The incidence of treatment emergent polycythaemia resulting in discontinuation of injectable TU in clinical studies carried out in United States and European Union was 1.8% (22); however, as an expected side-effect of testosterone treatment, less severe polycythaemia may be more frequent without requiring discontinuation of treatment. The present study confirms that mild polycythaemia is not unusual during TU injections, but is rarely severe and usually manageable by wider inter-injection spacing

with or without temporary suspension of TU treatment. No men in this study required venesection, anticoagulation or discontinuation of testosterone treatment.

In conclusion, TU injection is a generally safe and well-tolerated treatment. POME presenting as cough/syncope symptoms during TU injection is uncommon, occurring with about 2% of TU injections. It is rapid in onset, usually evident during or immediately after TU injection, and lasting for up to 10 min but resolving fully without serious sequelae. While it appears to be a random event, unrelated to age, underlying disease or which experienced nurse injector, based on inadvertent access of the oil vehicle to the venous system, its risk of recurrence exceeds chance. Haematoma after deep i.m. TU injection is rare even among men using antiplatelet or anticoagulant medications at the time of injection and while mild polycythaemia is relatively common, it is rarely severe or requiring specific treatment other than optimising inter-injection interval.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

In 2015 the Andrology department expects to receive support for an investigator-initiated study of testosterone pharmacology (Lawley) and testosterone and placebo drug supply for an investigator-initiated study of testosterone treatment (Besins).

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