THE INFLUENCE OF THE SOLVENT ON THE AVAILABILITY OF TESTOSTERONE PROPIONATE FROM OILY INJECTIONS

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Intramuscular injections of testosterone have only a transient biological effect, but that of its esters is prolonged, the duration increasing with increasing lipophilic nature of the ester. The obvious rate determining mechanism is the transfer, under the influence of distribution coefficient, from the oil solution in the muscle to the plasma, but there is evidence that this is rapid and is followed by storage elsewhere in the body, possibly fat, from which the drug is slowly discharged. We have sought to identify the rate determining process by administering testosterone propionate solution in 3 different solvents (isopropylmyristate, light liquid paraffin and n-octanol) intramuscularly to rats, and comparing elimination rates with the distribution coefficients between the solvents and water.

Carrier-free ^{14}C-testosterone propionate was prepared (To the labelled testosterone 0.2ml of pyridine and 1ml of propionic anhydride was added and heated on a waterbath for ≈4 hours. A small amount of water was added and acidified with glacial acetic acid, to acetylate the pyridine. The prepared testosterone propionate was extracted with benzene. The appropriate solvent was added after the evaporation of benzene.) and distributed between organic solvent and water at 37.8°. Distribution coefficients were determined by scintillation counting samples from each phase. The solutions involved were 'infinitely dilute', thereby eliminating association effects. Results are shown in Table 1.

Carrier ester was added to the injections, which were introduced into the right gastrocnemius muscles of male Wistar rats (250g). For muscle $t_{\frac{1}{2}}$ determinations, animals (dose 0.1mg) were killed at intervals and the ^{14}C activity at the injection site was determined. In other experiments, urine was collected from rats (i.m. dose 1mg) at 24h intervals. Counting procedures for both are described elsewhere (James et al 1969). Elimination rates of ^{14}C from muscle were first order, while the ^{14}C content of the daily urine output decreased bimodally with time. Feather analysis of the urine results revealed an initial first order elimination phase. Half-lives of both processes are given in Table 1.

The results show that the half-lives in muscle follow the same rank order as the distribution coefficients, as would be expected. The half-lives obtained from the ^{14}C urinary levels are significantly longer than those for muscle elimination and do not vary from solvent to solvent. It may therefore be inferred that absorption from an intra-muscular depot is not the rate-determining step controlling duration of biological action and probably occurs by release from another depot.

Table 1. Distribution coefficients and half lives.

Solvent	Distribution coefficient solvent/water x 10^3	Elimination half lives (h)	
		Muscle	Urine
Octanol	5.3	22.3	36.7
Isopropylmyristate	4.2	18.0	34.3
Light liquid paraffin	1.4	5.4	33.4

James, K.C., Nicholls, P.J. & Roberts, M. (1969) J.Pharm.Pharmacol. 21 24-27.

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