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Dexamethasone bovine pharmacokinetics

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SUMMARY

Dexamethasone phosphate (DXM-PHO) is an ester which is quickly hydrolysed by the bovine and the dexamethasone (DXM) plasma half-life was 5.16 h. It has been demonstrated that 54 h after DXM-PHO injection, DXM concentrations were lower than 0.1 mg/ml.

Tritiated dexamethasone was also administered twice to an another young bull for metabolite investigation. The elapsed time required to recover, in plasma, half of the radioactivity injected was 8.8 h. Radioactivity recovery in the urine reached 36.4% and 22.6% for the first and the second injections respectively.

INTRODUCTION

Dexamethasone (DXM) and dexamethasone esters (phenylpropionate, sodium-phosphate, isonicotinate) are among the most potent fluorinated synthetic glucocoritcoids widely used in human and veterinary practice for their anti-inflammatory, anti-allergic and anti-rheumatic properties. For several years, it has been known that these compounds have also been illicitly administered as 'hormones' to improve the phenotype of beef cattle at the end of the fattening period (1, 2).

The accumulation of such molecules and their metabolites in organs and meat could represent a potential hazard for the consumer's health which is still difficult to evaluate. Investigations of residues (in plasma and urine) are not easy due to the many interfering compounds resulting from general metabolism of the animal. Moreover, other factors such as the misreading of the drug, the low quantities injected, the number of treatments, the delay between the injection and slaughtering and the nature of the treatment (intramuscular, intravenous, or others) can considerably affect the possibilities of detecting traces of these molecules.

This paper describes the study, by radioimmunoassay (RIA), of the DXM sodium-phosphate (DXM-PHO) pharmacokinetics in young cattle. Plasma half-life of the DXM, liberated from the ester, and the period in which DXM is still detectable have been determined. In further investigations on DXM metabolism, tritiated DXM was administered to another bull. Pharmacokinetics of the total radioactivity (tritiated DXM + related tritiated compounds) have also been studied and recovery of radioactive compounds from the urine was assessed.

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MATERIALS AND METHODS

Plasma DXM concentrations were determined by RIA following the method described by Lejeune-Lenain et

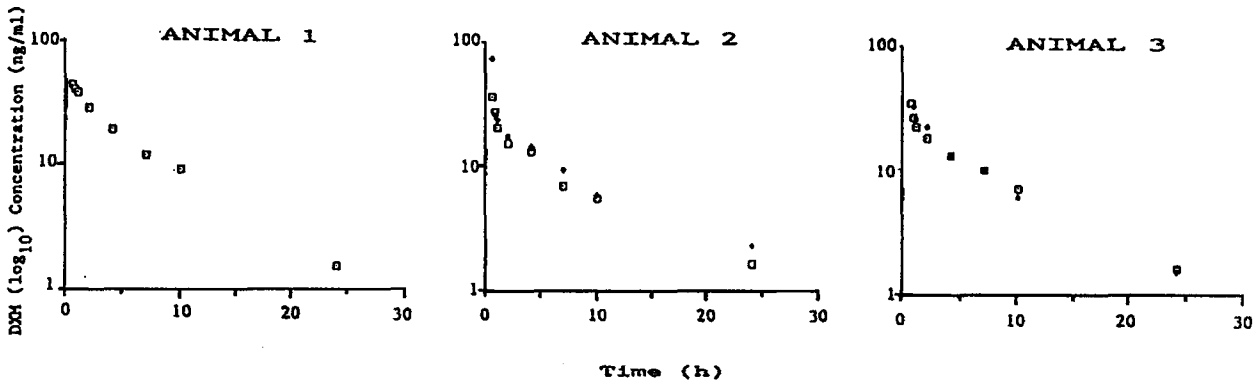

Fig. 1 : Semi-logarithmic plots of the disposition curve of dexamethasone phosphate in bovine plasma
Open squares – first injection, filled diamonds – second injection

al. (3). Cross-reactivities with the main endogenous steroids (including cortisol) were lower than 0.1%.

Chemicals

Dexamethasone (DXM) was purchased from Steraloïds, the monoclonal antiserum against DXM, from IgG Corporation (Nashville, USA) and dexamethasone-21-Na-phosphate (DXM-PHO), (Decadron) from Merck Sharp and Dohme (Germany). Labelled 1,2,4-[^{3}H]-DXM was purchased from Amersham (UK: code number = TRK 417).

Animals

Two young Pie-Noir bulls weighing 280 kg (animal 1, experiment I) and 235 kg (animal 4, experiment II) and identical Pie-Noir cattle twins weighing 124 kg (animal 2, experiment I) and 132 kg (animal 3, experiment I) were placed in metabolism boxes and allowed hay, granules and water *ad libitum*.

Treatments and sampling

Decadron (0.1 mg/kg body weight) was injected in the left jugular vein and the animals were catheterized in the right jugular vein to minimize disturbances during blood sampling. Blood samples (10 ml) were collected at frequent intervals on the first day, put into ice-cold heparinized tubes and immediately centrifuged.

Animal 4 was injected first with 400 µCi of tritiated DXM and 9 days later with 483 µCi. Radioactive plasma and urine samples were directly transferred to scintillation vials. After addition of 10 ml of scintillation liquid (Lumagel), vials were counted for 10 min in a Beckman (No. LS 7500) β-scintillator. Blanks were collected from the same animal before treatment.

RESULTS AND DISCUSSION

Experiment 1: DXM-PHO in plasma

DXM plasma concentrations are shown in semi-logarithmic plots (Fig. 1). Maximum levels (> 700 ng DXM/ml plasma) occurred during the first 15 min following the administration. After 30 min, and for five consecutive experiments, DXM concentrations decreased very sharply and showed values ranging from 72–20 ng/ml plasma.

Semi-logarithmic regression analyses gave 5.46 h as the mean plasma half-life (SD = 0.26, n = 5).

In each experiment, DXM concentrations were below 0.1 ng/ml, 54 h post-injection. Pharmacokinetics were established on the basis of 8 DXM RIA values and each measurement was repeated 3 times.

In dairy cows, Fairclough et al. (4) demonstrated that a 20 mg DXM-PHO intramuscular injection led to 70–24 ng/ml plasma maximum levels within 2–20 min and DXM concentrations were lower than 0.15 ng/ml after 72 h.

The results of our study agree very well with those of Tainturier et al. (5), who calculated a 4.5 h plasma half-life after a 0.1 mg/kg DXM isonicotinate intravenous injection to dairy cows. In cattle, Toutain et al. (6) observed 5.58 and 4.5 h plasma half-life after DXM and DXM isonicotinate intravenous injection, respectively.

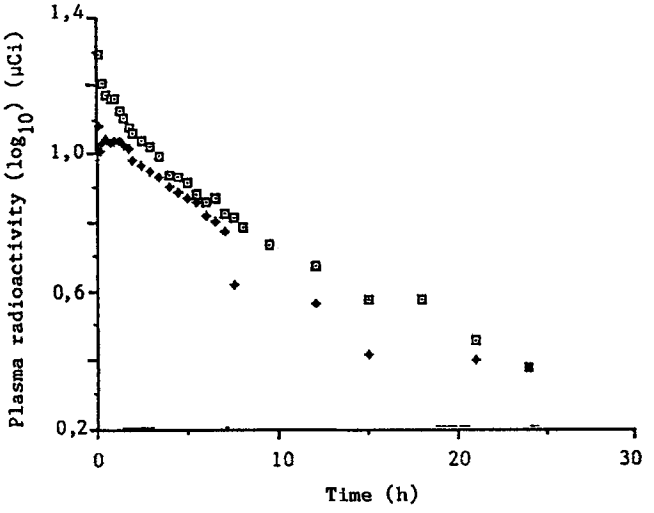

Fig. 2 : Semi-logarithmic plots of the elimination of radioactivity (DXM + related compounds) in bovine plasma
Open squares = first injection
Filled diamonds = second injection

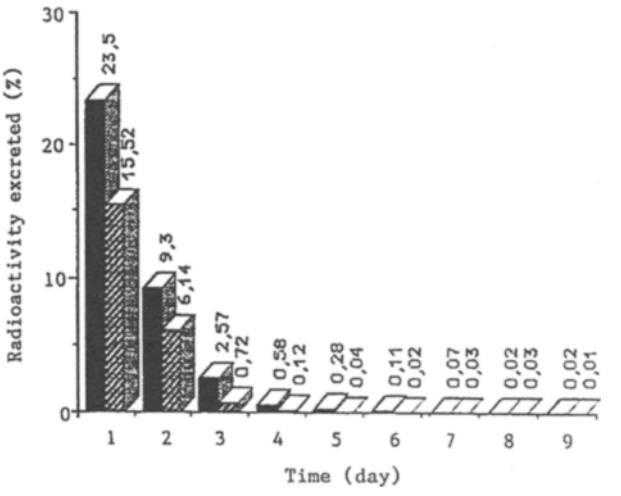

Fig. 3 : Radioactivity recovery in bovine urine following two intravenous injections of tritiated dexamethasone
Solid area = first injection
Hatched area = second injection

Experiment II: Tritiated DXM in plasma and urine

Pharmacokinetics I and II (on total radioactivity) were determined with 27 and 25 values respectively (Fig. 2).

Maximum radioactivity levels in plasma occurred during the first 15 min following the two injections and the residual radioactivity was estimated at 0.09 µCi (0.02% of 400 µCi administered) just before the second injection.

For both pharmacokinetics, the radioactivity levels declined very slowly to become insignificant (< 0.05 µCi), 11 days after the second treatment.

During the first 24 h, the elapsed time to recover half of the radioactivity was 8.8 h for both injections. This value, higher than that obtained for DXM, is a global measurement involving tritiated DXM and other related tritiated compounds produced, particularly DXM metabolites. In addition to the two blood sampling periods (9 and 12 days), urine samples were also collected in order to estimate the radioactivity excreted daily (Fig. 3).

The total cumulative radioactivity recovered in urine 216 h after the administration, was 36.4% (first injection) and 22.6% (second injection). The number and the identification of DXM metabolites will be reported later.

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