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Comparative Pharmacokinetics of [^{65}Zn]Zinc Sulfate and [^{65}Zn]Zinc Pantothenate Injected Intravenously in Rabbits

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Received March 14, 1980, from the **Laboratory of Biochemistry and ‡Pharmacology Jean Bernard Hospital, BP 577, 86021 Poitiers Cedex, France.* Accepted for publication December 12, 1983.

Abstract □ The pharmacokinetics of zinc sulfate were compared with those of a new zinc salt, pantothenate, in rabbits. Each salt was administered at a dosage of 3.3 μCi of zinc-65/kg of body weight. The measured pharmacokinetics of the two compounds responded to a two-compartment open model. The urinary elimination of the two salts was similar, as was their localization in the skin and fur, but zinc pantothenate was fixed by the liver to a lesser extent than was zinc sulfate.

Keyphrases □ [^{65}Zn]Zinc sulfate—intravenous administration to rabbits, pharmacokinetics □ [^{65}Zn]Zinc pantothenate—intravenous administration to rabbits, pharmacokinetics □ Pharmacokinetics—comparison of [^{65}Zn]zinc sulfate and [^{65}Zn]zinc pantothenate injected intravenously, rabbits □ Zinc salts—zinc sulfate and zinc pantothenate, comparative pharmacokinetics, intravenous administration to rabbits

Zinc sulfate is used to treat acrodermatitis enteropathica (1, 2), a condition associated with abnormal zinc metabolism. Zinc pantothenate, which we synthesized in our laboratory, had a much lower toxicity when administered orally to animals than did zinc sulfate and exhibited better gastric tolerance (3). We report here a comparative pharmacokinetic study of the intravenous injection of the two radioactive zinc salts.

EXPERIMENTAL SECTION

Reagents—[^{65}Zn]Zinc pantothenate was prepared as previously described (4). The principle of the reaction is an exchange between calcium pantothenate and [^{65}Zn]zinc sulfate with a specific radioactivity of 3.5 mCi/mg.

Animal Treatment—Six male rabbits (mean weight, 2.5 kg) were isolated in metabolism cages and placed on a water diet 12 h prior to the experiment. The necks of the animals were shaved, and a 0.5% solution of lidocaine was applied as a light topical anesthesia. The jugular vein was freed, and a catheter was inserted. Bleeding was prevented by placing a small sponge imbibed with anesthetic under the suture. The protruding catheter was fixed to the skin with a bandage, thus permitting both injection of the products tested and blood sampling.

Protocol and Analytical Procedures—Each zinc salt was injected into the jugular vein at a dose of 3.3 μCi of zinc-65/kg, and blood samples were taken at 5, 10, 15, 30, and 60 min and 2, 4, and 6 h postinjection. Blood samples (4 mL) were taken at the indicated times in a dry polypropylene tube (5), and serum was separated by centrifugation for 10 min at 3000 rpm. Animals were sacrificed 6.5 h after injection, and various organs or tissue fragments were removed and weighed: liver, kidneys, whole skin with fur, and, after washing with physiological saline, the small intestine.

Radioactivity was determined with a liquid scintillation counter[1]. Serum activity is expressed as disintegration per minute after quench correction (Fig. 1). For urine elimination and tissue and organ samples, the results are expressed as the percentage of the total quantity administered (Table I).

[1] Model 9000 γ; Beckman.

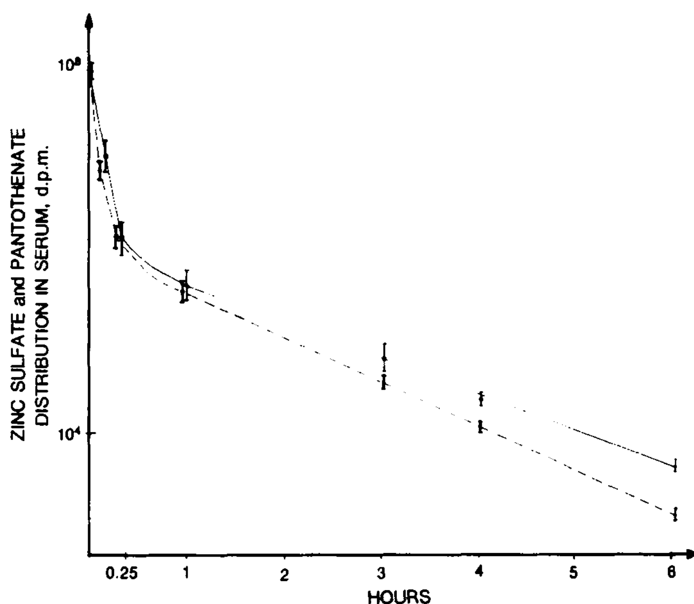

Figure 1—*Kinetics of the blood distribution of [^{65}Zn]zinc sulfate (—) and [^{65}Zn]zinc pantothenate (- -) after intravenous injection to six rabbits. The radioactivity is expressed as disintegrations per minute (d.p.m.). Results are expressed as the mean* ± SE.

RESULTS AND DISCUSSION

The pharmacokinetic data indicate that the distribution half-life (α) of zinc pantothenate is shorter (0.11 h^{-1}) than that of zinc sulfate (0.134 h^{-1}) (Fig. 1). Urinary elimination is very low and does not exceed 1% of the administered dose, which confirms results of previous studies with rats (6) and dogs (7) with zinc sulfate alone.

Both salts exhibit a similar distribution in the kidneys, the small intestine, the skin, and the fur. In the present study, there is a clear difference in hepatic

Table I—Tissue Distribution and Urine Elimination of [^{65}Zn]Zinc Pantothenate and [^{65}Zn]Zinc Sulfate after Intravenous Administration [a]

Tissue or Fluid	Radioactivity, Percentage of Total	
	[^{65}Zn]Zinc Pantothenate	[^{65}Zn]Zinc Sulfate
Liver	8	17
Kidney	2	2
Whole skin and fur	4	2
Small Intestine	1	1
Urine elimination	1	1

[a] Results were obtained 6.5 h after administration to six rabbits; results are expressed as percentage of the total activity.

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binding of the two salts: the zinc sulfate is fixed to a greater extent than is the zinc pantothenate (17 *versus* 8%).

The efficient distribution and diffusion of zinc pantothenate in the skin and the fur, as well as its less important retention in the liver, would suggest a therapeutic use in the treatment of disorders of the skin and scalp.

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Epiandrosterone- and Dehydroepiandrosterone-3β-alkanesulfonates as Inhibitors of Mouse Glucose-6-phosphate Dehydrogenase Activity

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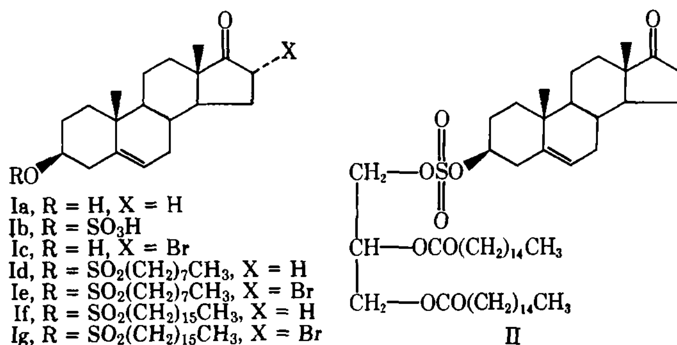
Abstract □ 3β-Alkanesulfonates of dehydroepiandrosterone, 16α-bromodehydroepiandrosterone, epiandrosterone, and 16α-bromoepiandrosterone were prepared in 54–95% yield *via* the reaction of long chain alkanesulfonyl chlorides with the corresponding dehydroepiandrosterone, and epiandrosterone analogues. These compounds inhibit mouse glucose-6-phosphate dehydrogenase activity.

Keyphrases □ 3β-Alkanesulfonates—synthesis, screened as glucose-6-phosphate dehydrogenase inhibitors □ Long-chain alkanesulfonyl chlorides—synthesis, antitumor agents

In a series of clinical and epidemiological studies several investigators have found that women with subnormal plasma concentrations of the adrenal steroid dehydroepiandrosterone (Ia) have a high risk of developing breast cancer (1–3). We have found that long-term treatment of various mouse strains with Ia inhibits the development of spontaneous breast cancer (4) and chemically induced lung (5) and colon tumors (6). It also blocks the 12-*O*-tetradecanoylphorbol-13-acetate (tumor promoter) stimulation of DNA synthesis in mouse epidermis (7) and inhibits the rate of [^{3}H]thymidine incorporation in various cell lines in culture (4).

Compound Ia is a potent noncompetitive inhibitor of mammalian glucose-6-phosphate dehydrogenase (G6PDH) (8, 9). Inhibition of this enzyme and the pentose-phosphate shunt, a major source of extramitochondrial NADPH, may account for the reduction in DNA synthesis rate by the steroid (10). Dehydroepiandrosterone in human plasma is largely sulfated. According to Oertel and Hoppe-Seyler, the predominant sulfated form of Ia in human plasma is not dehydroepiandrosterone sulfate (Ib), but an ester of Ib and a diglyceride, known as dehydroepiandrosterone sulfatide (II) (11). The sulfatide was found to be a more potent inhibitor of G6PDH than Ia (9).

We have observed that II is more effective than Ia in inhibiting mouse epidermal G6PDH as well as in blocking 12-*O*-tetradecanoylphorbol-13-acetate stimulation of DNA synthesis in mouse epidermis (7). On the other hand II is a labile material and decomposes readily within a few days, even



when stored at −5°C, to the sulfate Ib, resulting in loss of biological activity. Replacement of the sulfate functionality with sulfonate should lead to more stable analogues. In the search for stable and potent derivatives of II, we decided to incorporate the long chain alkanesulfonates into compounds which have already demonstrated a greater activity as inhibitors of glucose-6-phosphate dehydrogenase such as 16α-bromoepiandrosterone (7). Accordingly, 3β-alkanesulfonates of Ia, 16α-bromodehydroepiandrosterone (Ic), epiandrosterone (IIIa), and 16α-bromoepiandrosterone (IIIb) were prepared.

RESULTS AND DISCUSSION

Chemistry—3β-Alkanesulfonates of dehydroepiandrosterone and epiandrosterone (I and V) were synthesized by the reaction of a long chain alkanesulfonyl chloride IVa–e with the corresponding dehydroepiandrosterone or epiandrosterone analogue in the presence of dry triethylamine (Scheme I).

Long-chain alkanesulfonyl chlorides IVa–e were prepared in 60–85% yields from the corresponding fatty alcohol *via* a modification of the King and Aslam procedure (12) in which the hydroxyl group was replaced by the isothiuronium functionality and then the sulfur moiety was oxidized with chlorine in aqueous medium (Scheme II).

Biological Activity—The compounds listed in Table I were evaluated for their abilities to inhibit mouse epidermal glucose-6-phosphate dehydrogenase (Table II). Among the 3β-alkanesulfonates, compound Vf and its 16α-bromo analogue (Vg), both with the hexadecanesulfonyl side chain attached to the 3β-position of the epiandrosterone molecule, are the most potent inhibitors.

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