CLINICAL PHARMACOLOGY SECTION

Concentrations of the oxime 2-hydroxyiminomethyl pyridinium methyl methane sulphonate (P2S) after intramuscular injection in humans

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Intravenous pralidoxime mesylate (P2S) in the therapy of organophosphorus (O–P) poisoning is standard. In practice an intravenous injection might be impossible and the alternative intramuscular (i.m.) route may have to be used. Animal experiments have shown that, with atropine, plasma P2S concentrations of 4·0 μg/ml or greater are necessary for maximal therapeutic action. This study has been carried out to determine: (a) the intramuscular P2S dose necessary to produce quickly a plasma concentration of 4 μg/ml.; (b) the plasma P2S concentrations obtained on intramuscular injection in individuals on an oral regime of P2S; (c) what clinical side effects are produced.

To determine (a), three intramuscular doses of P2S (200 mg, 500 mg and 750 mg) were each given in 2·0 ml Water for Injection B.P. into the upper and outer aspects of the thigh to separate groups of volunteers (total fifty-five). Blood samples were obtained from the median cubital vein immediately before and at 10, 20, 30 and 60 min after injection.

To determine (b), under similar experimental conditions, these same doses were then given to a total of fifty-two volunteers 3 and 6 h after a single 4·0 g oral dose of P2S.

To determine (c), twenty-two volunteers received 3 intramuscular injections of 500 mg P2S at 20 min intervals after 4×4·0 g doses of P2S given at 6 h intervals. Plasma P2S concentrations were determined at the times stated above after the third injection. Note was made of any clinical side effects produced.

It was found that an intramuscular dose of 500 mg P2S or greater produced plasma P2S concentrations of 4·0 μg/ml within 5 minutes. Mean peak plasma concentrations of 4·9 and 6·3 μg/ml were obtained with the 500 mg and 750 mg dose respectively, 20 min after injection. Three hours after a 4·0 g oral dose of P2S, 500 mg and 750 mg P2S intramuscularly produced mean peak P2S plasma concentrations of 14·8 μg/ml and 16·0 μg/ml respectively, 20 min after injection; these same doses given 6 h after a single oral dose of P2S produced lower mean peak values of 9·8 and 11·9 μg/ml respectively.

Three intramuscular injections of 500 mg P2S given at 20 min intervals 3 h after the fourth oral P2S dose produced mean peak plasma concentrations of 23·9 μg/ml (16·2—33·9) 10 min after the third injection and P2S plasma concentrations were still above 7·0 μg/ml 3 h after the first injection. No untoward discomfort was experienced by the volunteers at the 500 mg dose level, but at 750 mg a dull ache at the injection site persisted for five to six hours.

Visual disturbances presenting as transient episodes of blurred vision and lasting from minutes to 1 to 2 h were experienced by fifteen of the twenty-two volunteers receiving three P2S injections. These occurred occasionally after the second injection but mainly after the third injection.