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BRIEF COMMUNICATION

Salbutamol and Quinterenol: Dipsogenic Action Produced by Beta-Adrenergic Stimulants[1]

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FALK, J. L. AND M. TANG. *Salbutamol and quinterenol: dipsogenic action produced by beta-adrenergic stimulants.* PHARMAC. BIOCHEM. BEHAV. 2(3) 413–415, 1974. – Subcutaneous injection of the beta-adrenergic agonists salbutamol and quinterenol produced a dose-related increase in water intake in water-satiated rats. These agents were approximately equal in dipsogenic efficacy and equivalent to isoproterenol, but less effective than diazoxide. The smaller cardiac stimulant action of salbutamol and quinterenol was probably responsible for their low lethality compared to previous results with isoproterenol.

Salbutamol Quinterenol Water intake Beta-agonist Drinking

SUBCUTANEOUS administration of the beta-adrenergic agonist isoproterenol produces a copious water intake lasting 2–3 hr in water-satiated rats [7]. This has been confirmed by other investigators [2, 4, 6] and extended to the structurally similar beta-agonists nylidrine and isoxsuprine [6,9], alpha-adrenergic blockers [9], and to diazoxide [3], an agent with complex activities which include beta-adrenergic stimulation. While neither dose-effect curves for drinking nor observations on lethality are available for nylidrine or isoxsuprine, at least two groups of investigators have noted a considerable incidence of debilitation and lethality following even small doses of isoproterenol [2,4]. In the interests of furthering the analysis of beta-adrenergically induced drinking without the complications of debilitation and mortality, we selected two beta agonists for study which appear to have a predominantly β_2 stimulant action, salbutamol [1] and quinterenol [10].

METHOD

Animals

Twelve, male, albino, Holtzman rats with a mean weight of 353 g (range: 339–377 g) at the beginning of the experiment, were housed individually in stainless steel cages in a temperature-controlled room with a 12 hr on and 12 hr off light cycle. They were divided randomly into 2 groups of 6 rats.

Drugs

Drugs were dissolved in 0.9% NaCl solution and were prepared just prior to injection. Doses are specified in terms of the salts. Salbutamol, 2-t-butylamino-l-(4-hydroxy-3-hydroxymethyl) phenylethanol, was obtained as a gift from Allen and Hanbury Research Ltd. Quinterenol, l-[5-(8-hydroxyquinolyl)]-2-isopropylaminoethanol, was obtained from Pfizer, Inc., through the courtesy of Dr. P. F. Moore.

Procedure

All animals were adapted to a food and water schedule for 3 days in which water was continuously available from water tubes (Richter type) and food (Purina laboratory chow, pelleted) was removed for 3 hr each day. At 1:00 p.m. each day, food was removed from the cages. Animals were weighed, water tubes were filled and hourly water intakes were measured for the next 3 hr (1:00–4:00 p.m.). Food was replaced at the end of the third hr. Scheduled drug injections were administered at the start of the 3-hr drinking period immediately after body weight determinations. It is important to note that they were not water deprived. One group (N = 6) received injections of salbutamol and the other group (N = 6) was injected with quinterenol. All injections were subcutaneous and made into the loose skin on the back. Animals were injected

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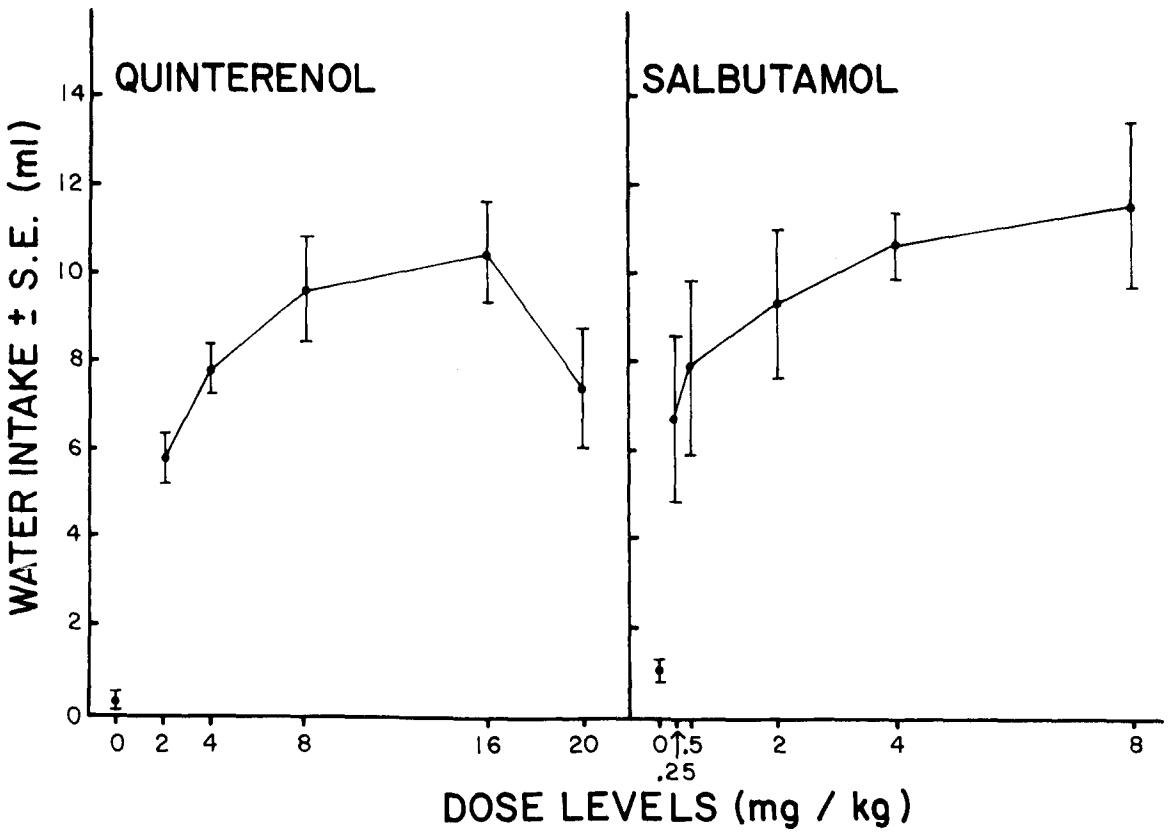

FIG. 1. Mean water intakes (3 hr) ± S. E. in water-satiated rats following subcutaneous injection of either salbutamol or quinterenol. 0 mg/kg = the placebo injection of 0.9% NaCl.

every third day and received either a particular dose of a drug or a placebo (0.9% NaCl). Each dose level or the placebo was administered once to each animal, with the treatment order for each animal determined by a randomizing procedure. The dose levels for quinterenol were 2, 4, 8, 16 and 20 mg/kg, and for salbutamol were 0.25, 0.5, 2, 4, and 8 mg/kg. Injection volume was a constant proportion of body weight for the various dosages and for the placebo and was always less than 0.5 ml.

RESULTS AND DISCUSSION

Figure 1 shows that both salbutamol and quinterenol induce a dose-related increase in water intake in water-satiated rats. These agents were approximately of equal efficacy in inducing water intake. They are approximately as efficacious in this regard as isoproterenol [7], but not as efficacious as diazoxide [3]. The drug effects were each analyzed for significance by an overall F-test (11, Pp. 105–139). For quinterenol, $F(5,25) = 19.88$, $p<0.01$, and for salbutamol, $F(5,25) = 15.96$, $p<0.01$. Tukey's test for differences between means shows that for quinterenol the difference between the 2 and 16 mg/kg doses was significant ($p<0.01$) and for salbutamol the difference between 0.25 and 8 mg/kg was significant ($p<0.05$). For quinterenol, the dose-effect function appears to descend at the 20 mg/kg point, although this difference from the 16 mg/kg level was not statistically significant. For salbutamol, one animal failed to drink at the 2 lower dose levels (0.25 and 0.5 mg/kg) which increased the variance at these points. The optimal dose would seem to be 4 mg/kg since the variance was small and fewer beta adrenergic side effects were evident. Pilot work at the 16 mg/kg dose yielded no further increase in drinking and led to occasional deaths. One death did occur at 8 mg/kg in those preliminary studies. In the case of quinterenol, no deaths occurred in the present study nor in the pilot work using doses up to 24 mg/kg. In similar studies on water intake using isoproterenol, death was a not uncommon occurrence following even small, subcutaneous doses [2,4]. The lack of lethality in the present experiment was probably due to the considerably smaller activity of these drugs as cardiac stimulants compared to isoproterenol [1, 5, 10].

For both drugs, most of the induced water intake occurs during the first 2 hr of the 3-hr drinking period as it does in the case of isoproterenol [7]. It is interesting that salbutamol does not appear to have a more prolonged dipsogenic action than isoproterenol since isoproterenol is inactivated by catechol-0-methyltransferase while salbutamol is not [8].

This study confirms the beta-adrenergically induced drinking observed with other beta-stimulating drugs [6, 7, 9]. Salbutamol and quinterenol have the advantage of low lethality risk so that valuable animals may be repeatedly tested with these agents.

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