# Hyperglycemic and Hyperlactic Acidemic Effects of Soterenol (MJ 1992) (34286)

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(Introduced by R. C. Ellingson)
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Soterenol [2-hydroxy-5-(1-hydroxy-2-isopropylaminoethyl) methanesulfonanilide hydrochloride], previously identified as MJ 1992, is a member of the alkylsulfonamidophenethanolamine series of compounds introduced by Larsen and Lish (1). These compounds display pharmacologic actions similar to those exhibited by the phenolic phenethanolamines. Certain members of the series are, in addition, effective catecholamine antagonists (1–3).

Dungan *et al.* (4) reported that in several animal species soterenol is a highly effective bronchodilator possessing both potent $\beta$-adrenergic and weak $\alpha$-adrenergic stimulant properties. While soterenol is qualitatively similar in action to isoproterenol, several important pharmacologic differences have been observed. Thus, in comparison with isoproterenol, soterenol exhibited a longer duration of action, produced less pronounced cardiovascular effects, and did not elicit secondary bronchoconstriction. Additional data in support of these observations were described by Cho *et al.* (5) utilizing an experimental locked-lung model in dogs.

Since soterenol and isoproterenol display similar pharmacologic actions, it was of interest to determine if certain of the biochemical effects of these agents also were similar. The present report describes the hyperglycemic and hyperlactic acidemic effects of soterenol in comparison with isoproterenol in fasted rats.

*Methods.* Harlan male rats (140–200 g) fasted for 18 hr were used in all studies. Animals were anesthetized with pentobarbital sodium (30 mg/kg ip) 30 min prior to removal of blood samples from retro-orbital vessels by means of a capillary pipette.

In the dose–response study, blood samples were obtained immediately before and 60 min after intraperitoneal injection of *dl*-soterenol HCl or *dl*-isoproterenol HCl (doses refer to the free base). In the antagonism study with sotalol HCl, blood samples were removed immediately before oral administration of either water or sotalol, 60 min later immediately preceding intraperitoneal injection of soterenol or isoproterenol, and 60 min post soterenol or isoproterenol.

Blood glucose was determined by diluting whole blood 1:10 with 0.9% NaCl–2.0% NaF and analyzing the diluted specimen in the AutoAnalyzer utilizing the ferricyanide technique (6). Blood lactate was determined enzymatically in the AutoAnalyzer without a dialyzer using L(+)-lactic acid dehydrogenase (7).

*Results.* Intraperitoneal administration of either soterenol or isoproterenol elicited dose-related hyperglycemic and hyperlactic acidemic responses in anesthetized, fasted rats (Figs. 1 and 2). The hyperglycemic effect of these agents was dose-related only at doses below 0.025 mg/kg. Doses greater than 0.025 mg/kg produced maximal glucose responses. The hyperlactic acidemic response of the test drugs, however, continued to increase with the dose.

Interpolation of data in Fig. 1 and 2 indicates that 0.010 mg/kg of soterenol or 0.024 mg/kg of isoproterenol is required to induce a 20 mg/100 ml rise in blood glucose. Similarly, 0.070 mg/kg of soterenol or 0.14 mg/kg of isoproterenol is required to produce a 20 mg/100 ml increase in blood lactate.

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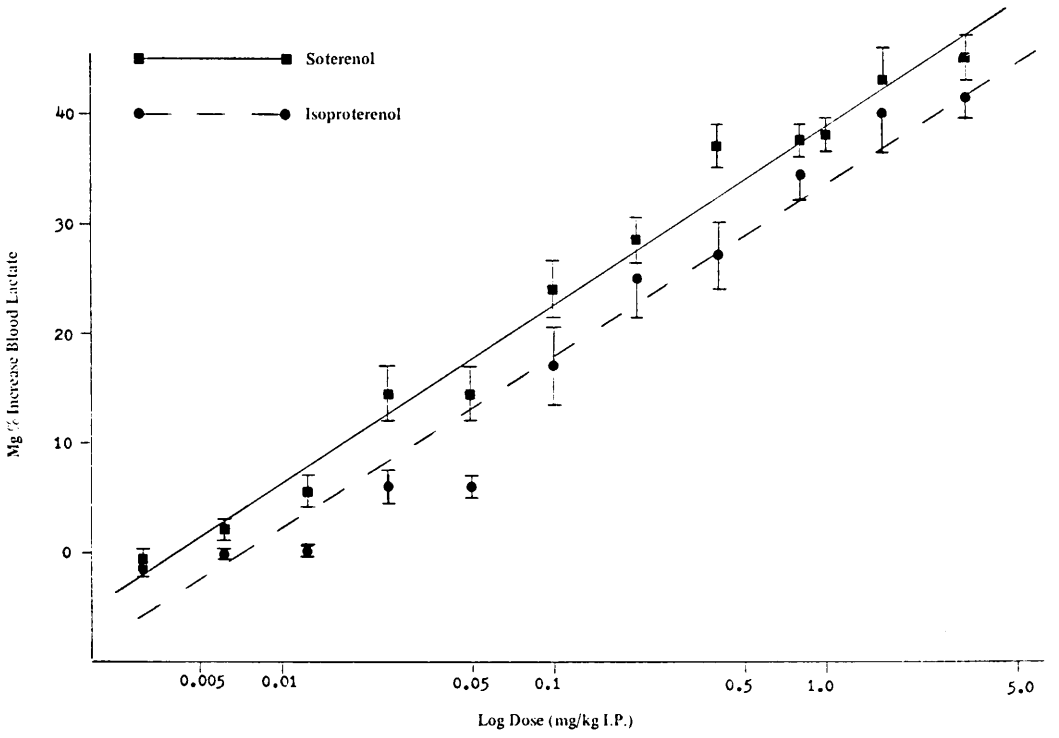


FIG. 1. Hyperglycemic effect of soterenol and isoproterenol in anesthetized, fasted rats; each point is the mean value obtained from 9 to 20 animals; vertical lines represent ±1 SEM.

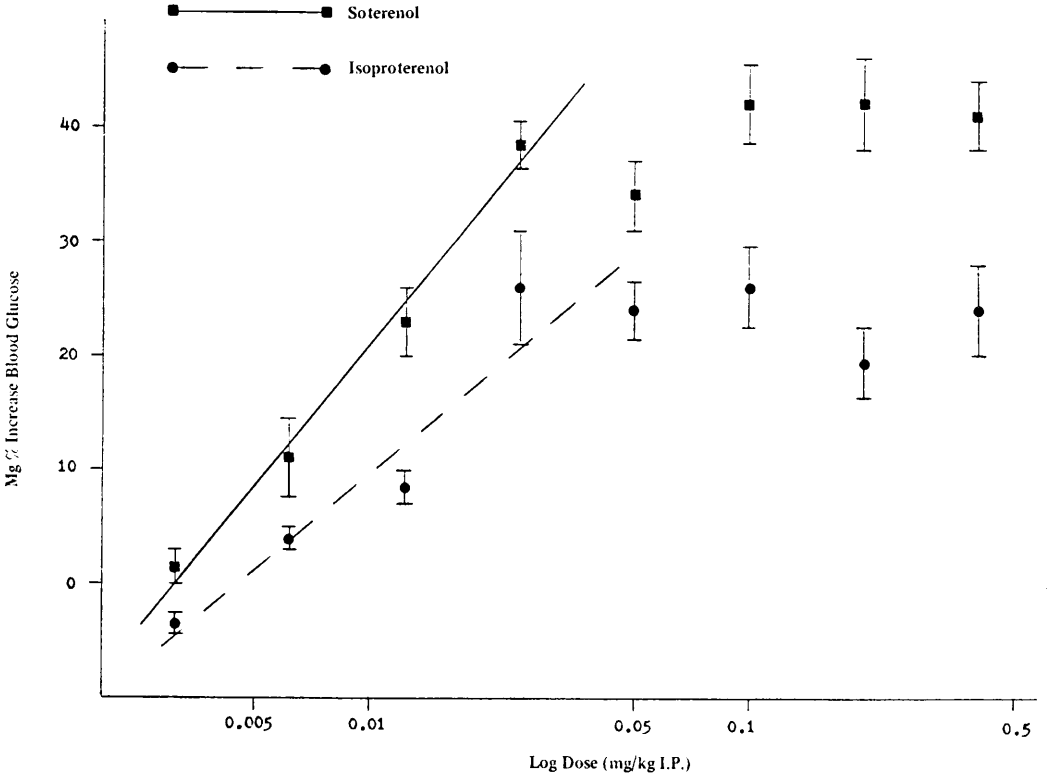


FIG. 2. Hyperlactic acidemic effect of soterenol and isoproterenol in anesthesized, fasted rats; each point is the mean value obtained from 9 to 20 animals; vertical lines represent ±1 SEM.

TABLE I. Antagonism of the Metabolic Effects of Soterenol and Isoproterenol by Sotalol.

| Treatment | | Mean increase in blood glucose and blood lactate (mg/100 ml ± SE) after oral pretreatment with | | | | | |
|---|---|---|---|---|---|---|---|
| | | Water (5 ml/kg) | | Sotalol (1 mg/kg) | | Sotalol (3 mg/kg) | |
| Drug | Dose (mg/kg; ip) | Glucose | Lactate | Glucose | Lactate | Glucose | Lactate |
| Soterenol | 0.05 | 39.4 ± 4.4 (8)[a] | 16.9 ± 2.2 (8) | 20.0 ± 5.0[b] (8) | 7.4 ± 1.7[b] (8) | 19.6 ± 3.9[b] (8) | 1.6 ± 0.6[b] (8) |
| | 0.20 | 44.2 ± 2.1 (14) | 34.0 ± 3.2 (14) | 42.6 ± 2.1 (14) | 22.2 ± 3.3[b] (14) | 40.0 ± 2.6 (7) | 13.0 ± 1.8[b] (7) |
| | 0.80 | 37.9 ± 3.9 (14) | 36.9 ± 1.5 (13) | 39.9 ± 2.5 (14) | 39.5 ± 2.0 (14) | 39.0 ± 8.1 (6) | 41.7 ± 3.4 (6) |
| | 3.20 | 27.1 ± 2.8 (14) | 42.1 ± 2.4 (14) | — | — | 25.6 ± 3.0 (7) | 47.5 ± 3.9 (7) |
| Isoproterenol | 0.05 | 28.5 ± 2.9 (11) | 6.0 ± 1.2 (11) | 15.2 ± 4.2[b] (6) | 4.2 ± 1.0 (6) | — | — |
| | 0.20 | 33.7 ± 3.1 (7) | 26.3 ± 2.9 (7) | 27.1 ± 4.9 (7) | 15.2 ± 2.0[b] (7) | 23.2 ± 3.3[b] (5) | 4.9 ± 3.7[b] (5) |
| | 0.80 | 36.1 ± 4.6 (7) | 38.8 ± 2.7 (7) | 44.2 ± 3.4 (6) | 43.4 ± 5.3 (6) | 38.4 ± 4.7 (7) | 23.2 ± 4.3[b] (7) |
| | 3.20 | 37.3 ± 4.1 (6) | 49.9 ± 3.0 (6) | — | — | 43.0 ± 3.9 (7) | 52.0 ± 2.7 (7) |

[a] Number of animals used is given in parentheses.
[b] Significantly different from water controls ($p < 0.05$).

Thus soterenol is approximately twice as effective as isoproterenol in producing hyperglycemia and hyperlactic acidemia in fasted rats.

Oral pretreatment with the β-adrenergic blocking agent, sotalol, significantly antagonized soterenol- or isoproterenol-induced hyperglycemia and hyperlactic acidemia (Table I). The metabolic effects of both drugs were attenuated in a similar manner by sotalol.

*Discussion.* Soterenol has been described in animal studies (4) as a highly potent β-adrenergic stimulant with activity equal to or greater than that of isoproterenol, the β-adrenergic prototype. The present results support these observations since soterenol elicited metabolic effects nearly identical to those of isoproterenol.

Classification of the adrenergic receptor site involved in catecholamine-induced hyperglycemia in rats cannot be categorized as either α or β (8, 9). However, Fleming and Kenny (8) showed that the use of fasted rats favors the hyperglycemic response to drugs acting on β-receptors. On the other hand, catecholamine-induced hyperlactic acidemia was described as a relatively pure β-stimulatory response (9–11). Previous studies demonstrated that sotalol blocks the hyperglycemic and lactic acidemic effects of isoproterenol in fasted rats (11–13).

With the exception of small quantitative differences, our results demonstrate that the hyperglycemic and hyperlactic acidemic effects of soterenol were virtually indistinguishable from those of isoproterenol. In addition the metabolic responses to both agents were attenuated to a similar degree by sotalol. Thus our data indicate that these metabolic effects of soterenol are mediated by activation of β-receptors.

*Summary.* Soterenol produced hyperglycemic and hyperlactic acidemic responses in the fasted rat nearly identical to those elicited by isoproterenol. The metabolic effects of both drugs were antagonized similarly by sotalol.

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