Absorption and Elimination Profile of Isoproterenol I

Anesthetized Dogs

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Tachycardia has been used as an indirect measure of isoproterenol absorption in anesthetized dogs. It was rapidly absorbed by the mucous membrane of the small intestine, proximal colon, and rectum and best absorbed by the mucous membrane of the trachea. A ratio of approximately 7:1 was obtained when the activity from the trachea and rectum was compared. Isoproterenol was poorly absorbed in the empty stomach when the mucosal surface was at pH 1.5–4.0. The cardiac response to intravenous injection or infusion of isoproterenol through the femoral and the gastro-epiploic (portal) veins has been compared. A statistically significant and greater increase in the heart rate was obtained consistently from the femoral vein. This difference may be attributed to some inactivation of isoproterenol by the portal-hepatic system.

ISOPROTERENOL [1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol HCl], a sympathomimetic amine, has been used extensively in the treatment of bronchial asthma and other bronchopulmonary diseases. Segal and Beakey (1) and Gay and Long (2) obtained satisfactory results in man by administering the drug by aerosol inhalation. Gay and Long (2) also reported the efficacy of oral medication. In addition to the treatment of asthmatic disorders, isoproterenol has been reported useful in the symptomatic treatment of heart block (Adams-Stokes syndrome). Nathanson and Miller (3), Prinzmetal and Kennamer (4), and Schamacher and Schmock (5) reported the satisfactory results obtained by sublingual administration of the drug. Burchell (6) and Robinson (7) obtained good therapeutic results by rectal medication. An intravenous infusion was reported effective by Penton *et al.* (8), Jones (9), and Zoll and Linenthal (10).

These and other similar reports describing the various routes of medication with isoproterenol have prompted the authors to establish the absorption profile of this drug. Results obtained in dogs are presented in this communication.

MATERIALS AND METHODS

Aqueous solutions of isoproterenol, 1-(3,4-dihydroxyphenyl) - 2 - isopropylaminoethanol HCl, were prepared fresh prior to medication. All doses are in terms of the base unless indicated otherwise.

A total of 35 mongrel dogs, weighing 10–15 Kg., were anesthetized with sodium pentobarbital,[1] 30 mg./Kg. i.v., followed by morphine sulfate, 5 mg./Kg. i.m., approximately 30–40 min. after anesthesia. Additional anesthesia was administered whenever needed.

Heart rate was monitored by means of an electrocardiograph (Viso-Cardiette, Sanborn) using the Lead I attachment. Food was withheld 17–18 hr. prior to medication in the dogs used to measure the effect of increasing gastric pH and of the direct portal administration on the absorption of isoproterenol.

Intratracheal Instillation.—A small incision was made in the neck, and the trachea was exposed. A fine polyethylene catheter (PE 50) was introduced into the trachea through a tiny opening made through the cartilage 4–5 cm. below the larynx. Isoproterenol hydrochloride in doses of 8, 32, and 128 mcg./Kg. made up in a constant volume of 0.25 ml. was instilled into the trachea. Heart rate was monitored before and every 2 min. for the first 10 min. and every 5–10 min. thereafter for 60–90 min. after medication.

Intragastric Administration.—Isoproterenol was administered through a catheter which was implanted into the stomach in either of two ways. One was a direct method, as described by Lands (11) for intraintestinal administration. The other was to introduce a small polyethylene catheter into the stomach through a small incision made in the wall of the esophagus at the neck. In both cases the pyloric sphincter was ligated. A 15-mg. dose of isoproterenol in a volume of 3 ml. was administered followed by 2 ml. of water rinse. In addition, some dogs received solutions of Na_2CO_3–$NaHCO_3$.

Intraduodenal and Intracolonic Administration.—The procedure used was essentially the same as that reported by Lands (11). Solutions of 0.1–0.4-mg./Kg. doses of isoproterenol were administered in the same manner described above.

Rectal Administration.—Isoproterenol in doses of 0.032, 0.128, and 0.512 mg./Kg. prepared in a 0.25-ml. volume of distilled water was instilled into the rectum. Doses of 0.032 and 0.128 mg./Kg. were tested in the same dogs in which the tracheal absorption was observed.

Intravenous Administration.—Through a small polyethylene catheter placed in the saphenous vein, isoproterenol in doses of 0.1–0.4 mcg./Kg. was injected intravenously. The increase in heart rate was monitored until it returned to premedication rate.

Injection and Infusion of Isoproterenol Through the Femoral Vein and the Gastro-epiploic Vein.—They were carried out through fine polyethylene catheters (PE 50) that had been inserted previously

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[1] Marketed as Pentobrocanal.

TABLE I.—INCREASES IN HEART RATE OF ANESTHETIZED DOGS FOLLOWING ADMINISTRATION OF ISOPROTERENOL

Administration Route	Dose, mcg./Kg.	Experiments, No.	Onset, min. Mean (Range)	Response Max. Increase, Mean % ± S.E.	Time Max. Effect,[a] min. Mean (Range)
Trachea	8.0	10	3 (2–6)	19 ± 3	8 (4–25)
	32.0	10	3 (1–6)	53 ± 6	10 (6–30)
	128.0	10	3 (1–4)	104 ± 10	18 (8–30)
Small intestine	100.0	6	2 (1–3)	37 ± 8	9 (4–20)
	200.0	6	2 (1–3)	49 ± 7	11 (6–26)
	400.0	6	2 (1–6)	65 ± 32	17 (2–30)
Proximal colon	200.0	6	<1	22 ± 6	14 (1–60)
Rectum	32.0	6	2 (1–6)	15 ± 3	3 (2–6)
	128.0	6	1.5 (1–4)	40 ± 4	8 (1–15)
	512.0	6	1	65 ± 16	7 (2–15)
Stomach	15.0 mg. total dose	9	4, 6[b]	9, 28	8, 9
Intravenous, rapid injection	0.1	4	0.5	71 ± 12	1.5
	0.2	4	0.5	98 ± 17	1.0
	0.4	4	0.5	130 ± 15	0.8

[a] Experiments terminated before heart rate had returned to the premedication level in many experiments. [b] No response observed in seven of nine experiments.

into the femoral and the gastro-epiploic veins. The abdominal midline incision approach was used to insert a catheter into the visceral vein. Solution of isoproterenol, with the usual preservatives, in a dose of 0.4 mcg./Kg. was injected rapidly. A dose of 0.08 mcg./Kg./min. was infused for 30 min. by means of a pump. The order of injection or infusion at the two sites was alternated.

RESULTS

Absorption from the Trachea.—In 10 dogs a dose-related increase in heart rate was observed within 3 min., and the maximal rate was attained in 8–18 min. following medication (Table I, Fig. 1). Tachycardia caused by the largest dose lasted more than 90 min. As shown in Fig. 2, the biological efficiency from the trachea was more than four times that from the rectum, suggesting greater absorption or less destruction of the drug from this site.

Absorption from the Stomach.—In nine dogs with the pyloric sphincter ligated and the stomach practically empty, absorption of isoproterenol in a total dose of 15 mg. was determined. Only two of nine dogs tested showed a maximum increase in heart rate of 9 and 28% (Table I). When the terminal pH of the stomach of these animals was determined, it ranged from 1.5–4.0. The higher pH readings were obtained from the two dogs that showed slight tachycardia.

Since it generally is known that the pH of the absorbing surface greatly affects the ionization and absorption of various drugs, it was decided to test the effect of increasing gastric pH on the absorption of isoproterenol. In preliminary tests on four dogs, a slight to moderate increase in the heart rate, indicating absorption, was observed in three out of four dogs tested. As shown in Fig. 3, in the dog which registered no increase in the heart rate for 10 min. following medication with a 15-mg. dose of isoproterenol, there was an increase within 1 min. after an administration of 10 ml. of Na_2CO_3 solution (5%). This increase in heart rate reached the maximum of 63% in the following 10 min. It was still considerably above the premedication heart rate 60 min. following medication. The above observation indicated that alkalinization of the gastric content had caused an absorption of isoproterenol which was not evident before administration of an alkaline solution. The pH of the gastric fluid, aspirated in a small quantity through the catheter, during active absorption was approximately 10 compared with a pH of 3–3.5 determined prior to administration of the alkaline solution. The terminal pH of the gastric content as well as the mucosal surface of the

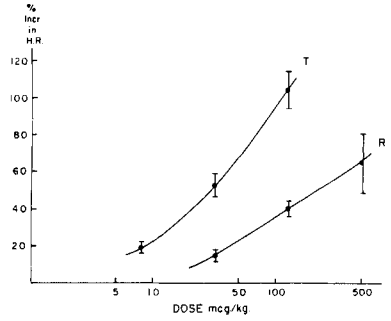

Fig. 1.—Comparative dose-response curves after tracheal (T) and rectal (R) administration of isoproterenol. Mean ±S.E. values of six to 10 dogs/dose level.

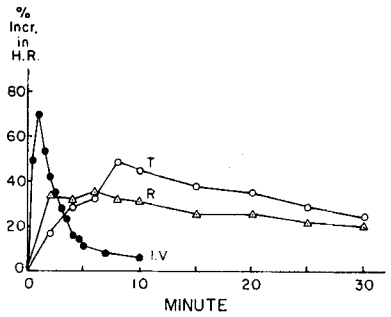

Fig. 2.—A comparison of the change in heart rate in dogs following the intravenous administration (i.v.) of 0.1 mcg./Kg. of isoproterenol with that following intratracheal (T) or rectal (R) administration of 32 mcg./Kg. and 128 mcg./Kg., respectively.

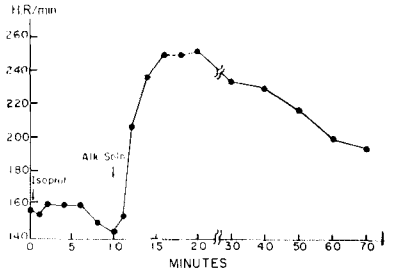

Fig. 3.—Effect of alkaline solution on the gastric absorption of isoproterenol in the anesthetized dog with the pyloric sphincter ligated. A dose of 15 mg. of isoproterenol was administered at the beginning followed by 10 ml. of 5% Na_2CO_3 at the tenth minute as indicated by the arrows. The initial gastric pH was 3–3.5 compared with pH of 10–10.5 on termination.

stomach determined at the end of the experiment was 10–10.5, as observed earlier.

In three dogs, the same experimental procedure was repeated, except that 10 ml. of a buffer mixture of 3% Na_2CO_3 and 7% $NaHCO_3$ solution (pH approximately 10) was administered 20 min. after isoproterenol medication. In two of three dogs tested, the heart rate increased to a maximum of 26–32% of the control rate in 6–10 min. following administration of an alkaline buffer. The pH of aspirated fluid obtained at 30 min. was 7.5–8 in either case compared with 3–3.5 taken before isoproterenol medication. The above alkaline pH was confirmed when direct measurement was made at termination of the experiment. No important increase in heart rate was obtained in the third dog despite an administration of the second 10 ml. of alkaline solution. The terminal pH of the gastric content and the mucosal surface was 3–4 in this case. These results seem to indicate that there was little or no absorption of isoproterenol when the pH of gastric contents was less than 3. In the dogs in which no increase in heart rate was observed after an administration of a 15-mg. dose of isoproterenol, the terminal gastric pH was found to be in the range of 1.5–3.5. On increasing the gastric pH (range 7–10), a considerable increase in absorption, as indicated by heart rate, was obtained.

Absorption from the Intestine.—In contrast to the poor absorption obtained from the stomach, in the same dogs good absorption was noted when the drug was introduced into the duodenal area (Table I). The pH of the mucosal surface ranged from 5.5–6. Differing from the stomach, isoproterenol was absorbed well through the mucosal wall of the small intestine, whereas at a comparable gastric pH, mucosal absorption was less. The presence of a greater surface in the intestine would favor absorption.

Absorption from the Proximal Colon.—The absorption pattern obtained from the colon resembles that obtained from the small intestine. There was a difference only in the degree of absorption, as reflected in a lesser increase in the heart rate obtained when the same dose (0.2 mg./Kg.) of isoproterenol was administered into the colon. These results (Table I) indicate that isoproterenol introduced into the gastrointestinal system will continue to be absorbed even after it is moved into the proximal colon.

Absorption from the Rectum.—In six dogs tested, an instillation of isoproterenol in doses of 0.032, 0.128, and 0.512 mg./Kg. caused an increase in heart rate within 1–2 min. in the majority of animals (Table I, Fig. 1). Although many experiments were terminated before the heart rate had returned to the premedication rate, with the larger doses the tachycardia lasted more than 30 min. It should be pointed out that the first two doses were tested in the same dogs that received isoproterenol intratracheally. Comparative dose-response curves obtained from the trachea and rectum are shown in Fig. 1. From these curves, the ratio of biological efficiency of greater than 7:1, favoring the trachea, was obtained. In general, the rate of absorption from the trachea was somewhat slower than from the rectum, and the duration of tachycardia initiated by the absorption of isoproterenol from the former was longer.

Intravenous Administration.—Rapid injection of isoproterenol in total doses of 0.1, 0.2, and 0.4 mcg./Kg. caused a linearly related increase in heart rate (Table I). However, sensitivity was found greater for the unanesthetized dog, as indicated by a larger response (16).

Comparison of the Heart Rate Effect of Isoproterenol Administered Through the Femoral Vein and the Gastro-epiploic Vein.—In both anesthetized and unanesthetized dogs, rectal administration of isoproterenol was more effective (tachycardia) than oral medication or direct intestinal instillation. Anatomically, the rectum supplies blood to both systemic and portal circulations through the hemorrhoidal plexus, whereas the entire venous circulation from the intestine reaches the heart indirectly by way of the portal system. Since the liver is known to metabolize various drugs including catecholamines, the aforementioned difference may be due to some inactivation of isoproterenol by the hepatic tissues.

To test this possibility, comparative studies have been carried out by administering isoproterenol (*a*) directly into the femoral vein and (*b*) into the gastro-epiploic vein, a small branch of the portal vein. The results are illustrated in Figs. 4 and 5. The femoral infusion of isoproterenol in a dose of 0.08 mcg./Kg./min. for 30 min. caused the heart rate to increase to a mean maximum of 38 beats/min. in 4–5 min., and thereafter it maintained a relatively steady rate of 25–32 beats/min. until the infusion was terminated. Mean maximal increases in heart rate recorded during the infusion were 25 ± 5, 32 ± 10,

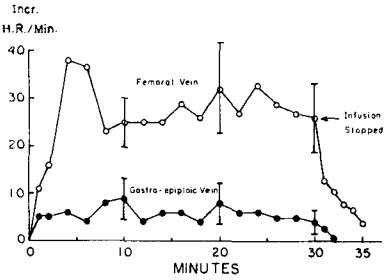

Fig. 4.—Effect of intravenous infusion of isoproterenol in a dose of 0.08 mcg./Kg./min. for 30 min. on the heart rate in anesthetized dogs (mean of four to five dogs).

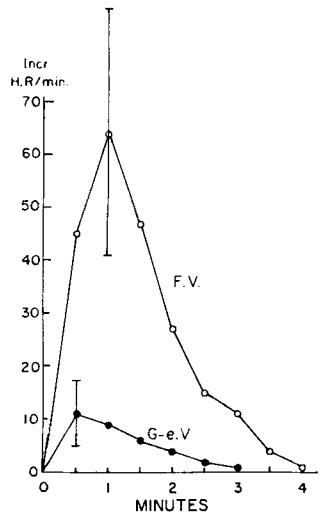

Fig. 5.—Effect of a rapid intravenous injection of isoproterenol in a dose of 0.4 mcg./Kg. on the heart rate in anesthetized dogs (mean of four dogs) Key: O, femoral vein; ●, gastro-epiploic vein.

and 26 ± 7 beats/min. at the 10-, 20- and 30-min. recording, respectively. The heart rate rapidly returned to the preinfusion rate (biological half-life of 1 min.) when the infusion was stopped. By contrast, the same dose of isoproterenol infused in the same manner through the gastro-epiploic vein caused only a small increase in the heart rate. Mean maximal increases of 9 ± 4, 8 ± 4, and 4 ± 2 beats/min. were recorded at the 10-, 20-, and 30-min. readings, respectively. As shown in Fig. 4, there was a statistically significant difference in the response of the heart to isoproterenol infused through these two sites. This difference was observed consistently in every dog tested.

A similar difference in the heart response was obtained after injection of 0.4 mcg./Kg. of isoproterenol. A mean maximal increase in the heart rate of 64 ± 23 beats/min. was obtained within 1 min. after femoral vein injection. A mean maximal increase of only 11 ± 6 beats/min. was obtained when the same dose of isoproterenol was injected through the gastro-epiploic vein (Fig. 5). This difference was consistent in every dog tested.

Four additional experiments were carried out in which isoetharine [1-(3,4-dihydroxyphenyl)-2-isopropylaminobutanol] was infused as described above. A dose of 5.0 mcg./Kg. was required to produce an increase in heart rate comparable with that obtained with 0.08 mcg./Kg. of isoproterenol. The difference between femoral and gastro-epiploic vein infusion was quite small (17.0% at maximum effect) with isoetharine, whereas with isoproterenol this difference was large (76%). The presence of an ethyl group on the carbon adjacent to the N has reduced markedly the loss of active product in the portal transit.

DISCUSSION

By using the increase in heart rate as an indirect measure of absorption of isoproterenol, the absorption profile of this sympathomimetic amine has been determined. Except for the stomach, in which the absorption was relatively poor, the intestinal tract, including the rectum, was found to absorb isoproterenol. Portmann *et al.* (12) have found that isoproterenol, in an aqueous solution of 1.7–15 mg. total dose, when administered orally to unanesthetized dogs caused an increase in heart rate which attained a dose-related maximum within 5 min. The approximate duration of the above effect was 120–240 min. Similar results have been observed in the anesthetized dog. The colonic absorption of isoproterenol is interesting in that it provides an explanation for a long duration of action of some sustained-release isoproterenol preparations. We have observed that in many instances a nondisintegrating medicinal tablet was delivered to the colon in 90–120 min.

It has been shown that isoproterenol is poorly or not absorbed in the empty stomach of the dog when the mucosal pH is 1.5–4. Isoproterenol has been reported by Lewis (13) to have an amine pKa of 9.87 ± 0.07 and a phenol pKa of 8.72 ± 0.05. A drug having these pKa's would have the amine function ionized at a pH of 7 or less. Schanker *et al.* (14) and Hogben *et al.* (15) have shown both in rats and man that a drug which is highly ionized in the acid gastric contents is not absorbed, but in the alkaline medium, its absorption is markedly facilitated. In the preliminary study, administration of a strong alkaline solution into the stomach which was passive to the prior administration of isoproterenol promptly caused an increase in the heart rate indicating absorption. The pH of a sample of gastric contents obtained by aspiration during tachycardia and at the end of the experiment was 10–10.5. At this pH, the phenol function is essentially ionized, whereas the amine function is greater than 50% unionized. This observation suggests that, under normal condition, absorption of orally administered isoproterenol in the stomach would be very small.

The pattern of absorption of isoetharine, an isoproterenol-like compound, has been reported by Lands (11). When the absorption profiles of these two closely related compounds are compared, there are striking similarities. Both compounds were readily absorbed by the mucous membranes of the trachea and gastrointestinal tract of the dog. Isoproterenol, however, showed greater activity from the mucous membrane of the trachea (approximately 7:1 ratio) than from the rectum; whereas isoetharine was about equally active from both sites of drug administration. This may indicate a greater stability of isoetharine than isoproterenol from various absorption sites. Absorption from the rectum reaches the heart partially by way of the portal system. Drugs may go through greater metabolic decomposition when circulated through the portal system to the heart.

This is supported by the observation that there is a relatively small difference between the response to femoral vein infusion of isoetharine, as compared with infusion into the gastro-epiploic vein, whereas in the case of isoproterenol there is a relatively large difference.

Intravenous injection of a small amount of isoproterenol (0.1 mcg./Kg.) caused an immediate increase in the heart rate lasting only 5–10 min. A similar observation was made in the unanesthetized dog (12). A relatively short duration of action indicates a rapid disappearance of active isopro-

terenol from the circulation as pointed out by Lands (11) regarding the similar intravenous behavior of isoetharine. The tachycardia-producing effect of isoproterenol, however, is 25 to 40 times greater than that of isoetharine.

In the later study on the absorption of isoproterenol in unanesthetized dogs, a greater tachycardia was obtained by rectal than by oral medication (12). A similar difference was observed in the anesthetized dog. Furthermore, this difference became more apparent when the cardiac response to tracheal administration of isoproterenol was compared with that of the intestinal or rectal administration. As stated earlier, the entire venous circulation from the intestine reaches the heart indirectly by way of the portal system, whereas part of the venous supply from the rectum reaches the heart directly through the systemic circulation. In the case of the trachea, all the venous supply reaches the heart directly through the superior vena cava. The passage of the drug through the portal circulation and the liver may make the above difference in the cardiac response. Jones and Blake (16), in their study on biological distribution of epinephrine in the dog, reported that the hepatic and portal circulation extraction of epinephrine was high (the ratios, 40–75%), our experimental results with isoproterenol have suggested a similar occurrence. Hertting and LaBrosse (17) infused 7-H^3-epinephrine into the systemic vein and the hepatic portal system in rats. Only 2% of the radioactive material was recovered from the urine as unchanged catecholamine following intraportal infusion, but 13.3% appeared in the urine after infusion into a peripheral vein. Portmann *et al.*, (12) have shown that the heart reflects quantitatively the presence of isoproterenol in the venous circulation to the heart. A significant reduction in the cardiac response when isoproterenol was injected or infused through the gastro-epiploic vein, a branch of the portal vein, suggested inactivation and/or increased metabolic conversion of isoproterenol by the portal system.

SUMMARY

By using the increase in heart rate as an indirect measure of absorption, the absorption profile of isoproterenol, a sympathomimetic amine, has been determined in the anesthetized dog. It has been shown that isoproterenol is poorly absorbed in the empty stomach when the mucosal surface is at pH 1.5–4.0. An administration of strong alkaline solution into the passive stomach promptly caused an increase in the heart rate, indicating absorption. The relationship between the gastric pH and the amine and phenol functions (pKa's) of isoproterenol has been discussed.

Isoproterenol was absorbed readily by the mucous membranes of the trachea and gastrointestinal tract. However, it was more active from the mucous membrane of the trachea. The activity ratio of approximately 7:1 was obtained when the activities from the trachea and rectum were compared.

The absorption of isoproterenol from the colon was similar to that obtained from the small intestine. The difference was in the degree of absorption or inactivation, causing lesser increase in the heart rate when the same dose (0.2 mg./Kg.) of isoproterenol was administered into the colon.

The cardiac response to intravenous injection or infusion of isoproterenol through the femoral vein and the gastro-epiploic vein has been compared. A statistically significant and greater increase in the heart rate was obtained consistently from the femoral vein. The difference may be attributed to some inactivation of isoproterenol by the portal-hepatic system when the drug was administered through the gastro-epiploic vein.

Intravenous administration of isoproterenol in graded doses produced a linearly related increase in heart rate.

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