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Systemic delivery of sympathomimetic amines by transdermal iontophoresis ☆

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Abstract

Certain sympathomimetic amines may be useful in the treatment or diagnosis of cardiovascular disease. However, obtaining sufficient blood levels of these drugs when given orally is difficult because of gastrointestinal destruction and their is a danger associated with intravenous administration. These problems have prompted the investigation of iontophoretic delivery of a novel sympathomimetic amine, KM-13, across the skin of anesthetized dogs. Dogs were monitored to determine cardiac rate or cardiac contractility. The KM-13 was dissolved in distilled H_2O to a concentration of 50 mM and placed in a 15 cm^2 matrix pad beneath the positive electrode of a DC constant current device. Delivered currents of 0.5–4.0 mA caused graded increases in cardiac contraction which reached a plateau within 20–30 min. In other dogs, delivery of 1 mA current for 15 min caused an increase in heart rate which peaked at about 24 min and decayed with a $T_{1/2}$ of approx. 95 min. Prior treatment of skin beneath the positive electrode pad with tolazoline (an α-adrenergic blocker) caused a more rapid response (peak with 15 min) and decay ($T_{1/2}$ of approx. 51 min) to KM-13. This study demonstrates that iontophoretic delivery of a sympathomimetic amine is feasible. Prolonged latency of onset and decay may cause problems in some uses. Prior use of vasodilators before applications of sympathomimetic amines can accelerate onset and decay.

Keywords: Sympathomimetic amine; Transdermal iontophoresis; Cardiotonic action

1. Introduction

Systemic delivery of drugs by transdermal iontophoresis (TI) has been proposed for administration of therapeutic or diagnostic agents whose physical properties preclude oral administration or passive transdermal absorption. Insulin, a protein hormone, may be given by TI when proper current type and pH are selected (Siddiqui et al., 1987). Smaller peptides such as luteinizing hormone-releasing hormone (LHRH) can also be effectively given by TI (Meyer et al., 1988). Additionally, systemic delivery of morphine by TI has been reported as a means of preventing pain following total hip replacement (Ashburn et al., 1992).

Certain sympathomimetic amines may be useful in the treatment or diagnosis of cardiovascular disease. The inability to obtain sufficient blood levels of these drugs when given orally because of

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gastrointestinal destruction, and the danger associated with intravenous delivery have prompted examination of iontophoretic delivery of sympathomimetic amines across the skin.

Preliminary experiments in our laboratory on the transdermal iontophoretic delivery of dobutamine, an often used catecholamine, were successful in eliciting only marginal and erratic cardiac contractility response in dogs. KM-13 is a new inotropic catecholamine with a chemical formula of *N*-[2-(3,4-dihydroxyphenyl)-ethyl]-1-methyl-3-(3-carbamoylphenyl)propylamine HCl; it exhibits pharmacological effects similar to those of dobutamine. However, KM-13 has been shown to be substantially more potent than dobutamine when administered by intravenous infusion (Caldwell et al., 1987). This higher potency makes iontophoretic delivery of KM-13 a viable method for the noninvasive administration of a catecholamine. The purpose of our studies was to determine the profile of hemodynamic effects of KM-13 delivered by transdermal iontophoresis.

2. Experimental model

2.1. Current-response relationships

Four dogs used for current-response studies were anesthetized with pentobarbital Na, 30 mg/kg i.v. and given supplemental doses as needed. They were fitted with catheters for measurement of cardiovascular variables, infusion of drugs i.v., and withdrawal of blood for plasma concentration of the sympathomimetic amine (Dixon et al., 1985; Sanderson et al., 1987). A Millar® transducer-tip catheter was introduced into the left cardiac ventricle for pressure measurement. This left ventricle pressure (LVP) signal was differentiated to yield LV dP/dt_{max}, a measure of cardiac contractility. The flanks of the dogs were shaved carefully for the application of electrodes (15 cm^2 area); no skin abrasions were beneath the electrode pads. The anode was a two-chambered device molded from polyvinyl chloride film. The upper chamber contained 1.8 M phosphate buffer (pH 5.8) gelled with karaya gum and glycerin. The lower chamber contained

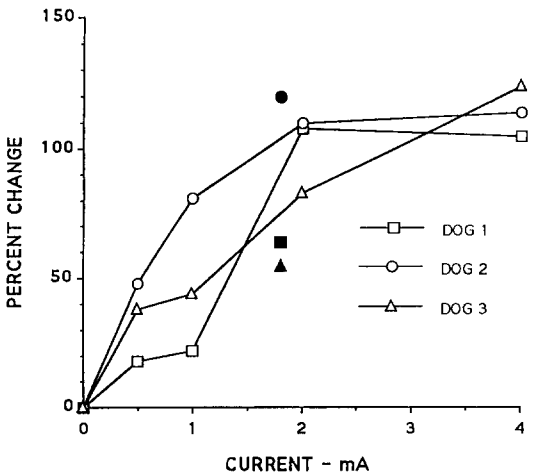

Fig. 1. Change (%) from baseline for cardiac contractility (LV dP/dt_{max}) vs current after 20 min of transdermal iontophoretic delivery of KM-13 for three dogs. Solid symbols (■,▲,●) indicate the contractility achieved following a 15 min i.v. infusion of 1 μg/kg per min of KM-13 in that dog.

2 ml of a 25 mg/ml (50 mM) solution of the hemisuccinate salt of KM-13. The chambers were separated by a Raipore 5035H anion exchange membrane. The lower chamber was enclosed by a Celgard 3501 microporous polypropylene membrane. An annular flange around the electrode was coated with Dow Corning 355 silicone adhesive. The cathode was a karaya gum pad containing 1.8 M phosphate buffer (pH 5.8). Current was applied at 0.5, 1, 2 and 4 mA for 20 min each at four consecutive intervals with a Phoresor® power supply. This method has been described in detail previously (Sanderson et al., 1987).

Blood samples were taken and plasma preserved as described by Dixon et al. (1985). About 3 h after the first experiment in each dog, the protocol was repeated for collection of another set of plasma samples.

2.2. Time-course studies

Another four dogs used for time-course studies were anesthetized with morphine SO_4 (2 mg/kg, i.m.) and pentobarbital Na (15–20 mg/kg i.v.) before they were fitted with a lead II ECG and electrode pads on their shaved flanks. Heart rate was monitored by a Grass cardiotachometer

triggered by the lead II ECG. Cardiac contractility was not monitored. The first anode pad was filled with either saline or a 0.2% solution of tolazoline, an α-adrenergic blocking agent. Current (1 mA) was applied for 15 min and then the pad was removed. A second anode pad containing KM-13 (25 mg/ml in H_2O) was then immediately applied to this same area and a current of 1 mA was applied for 10 min. Heart rate was monitored until any heart rate response completely decayed. A week following the experiment, the same dogs were reanesthetized and the experiment repeated. The two dogs which were given tolazaline as the first treatment were given saline, and vice versa. The same area on the flank was used for pad application.

2.3. Current-response relationships

Fig. 1 depicts the increase in cardiac contractility [left ventricular (LV) dP/dt_{max}] in response to the iontophoretic delivery of KM-13. Increasing the current from 0.5 to 4 mA caused progressive rises in LV dP/dt_{max} in all treated dogs. Three dogs reached a similar maximum change of approx. 100%. Another dog exhibited a substantially greater contractile response; LV dP/dt increases were 55, 442, 518, and 1050% for 0.5, 1, 2 and 4 mA, respectively. Fig. 1 also indicates the cardiac contractility response of three dogs to an intravenous infusion of 1 μg/kg per min of KM-13 (solid point). In all of the animals, the heart rate rose modestly in response to the iontophoretic infusion of the drug. No cardiovascular response was noted in any dog over a 30 min. period when the electrode system containing the KM-13 solution was in place without application of current.

Fig. 2 is a least-squares plot of the plasma concentration of KM-13 (C) vs the applied current (I) during iontophoresis. The open square points are the averages for four dogs at steady state, 15–20 min after initiation of the specified current. The error bars represent the standard deviations of these points. The line was generated from the results from the four dogs using four different currents at two separate times, each data point being treated independently. The

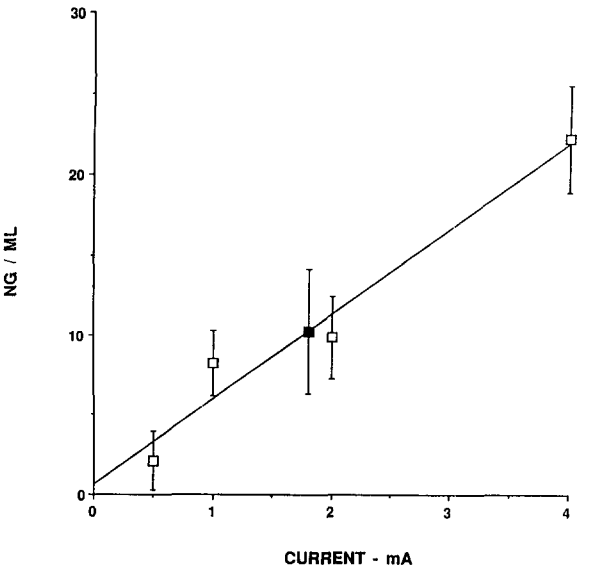

Fig. 2. Least-squares plot of the mean (±SD) plasma concentrations of KM-13 (□) vs the applied current after 20 min of iontophoretic delivery of KM-13. (■) Mean (±SD) plasma concentration of KM-13 at 15 min after an i.v. infusion of KM-13 at a rate of 1 μg/kg per min.

equation for the line is $C = 4.85I + 1.44$, with a correlation coefficient of 0.877. The solid square point and error bars represent the average and standard deviation, respectively, of the plasma levels of KM-13 after a 15 min intravenous infusion at a rate of 1 μg/kg per min. The point is placed on the least-squares line in order to show the current equivalent to that infusion rate. The current equivalent was approx. 1.8 mA. Note that the variability in blood levels from iontophoretic infusion is no greater than that from intravenous infusion.

Visual examination of the skin beneath the electrodes after the experiments revealed no skin damage apart from a very mild erythema noted on the skin of one dog.

3. Time course of effects

Earlier work on TI delivery of KM-13 indicated a considerable latency, approx. 5 min, before cardiovascular responses were evident. Depending on the current applied, 15–25 min were

required for peak effects to occur. Since high local concentrations of KM-13 at the site of TI and α-adrenergic vasoconstriction are expected with such concentrations, it was considered that local vasoconstriction may be limiting immediate assess of KM-13 to the systemic circulation. Therefore, in a separate series of experiments, an analysis of the time course was performed with and without local application of the α-adrenergic receptor blocker, tolazoline, which should block the vasoconstrictive actions of KM-13. Tolazoline administration itself had no effect upon heart rate.

In normal saline-pretreated skin areas, there was a moderate latency period of about 5 min before heart rate actions of KM-13 were evident during TI administration (Table 1). The time to peak effect was about 24 min. The average peak rise in heart rate was 74 ± 9 beats/min over baseline value. The $T_{1/2}$ for decay of heart rate was approx. 95 min. When KM-13 was administered by TI in the same area previously treated with tolazoline, there was a reduction in the latency period (approx. 2.7 min), time to peak effect (approx. 15 min) and the $T_{1/2}$ for heart rate response (approx. 51 min). Representative heart rate responses of one dog are illustrated in

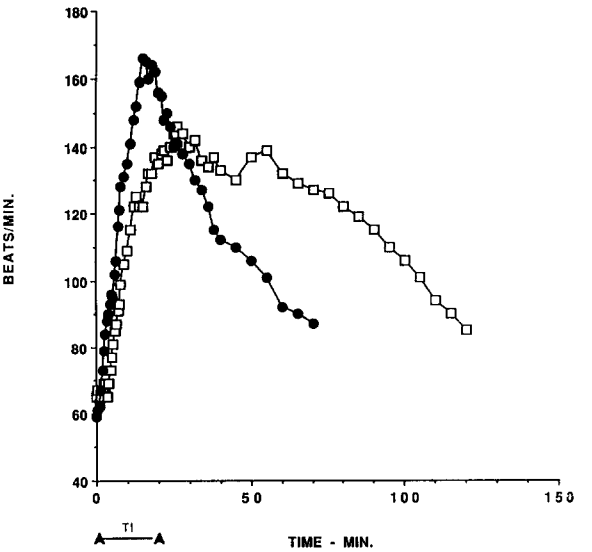

Fig. 3. Plots of heart rate responses over time of a representative dog to TI administration (0 to +10 min) of KM-13. One curve (□) was obtained after TI pretreatment of skin area with saline. The other curve (●), obtained 6 days later, in the same dog, was the response to KM-13 immediately after pretreatment with tolazoline.

Fig. 3. Although the peak rate change was higher with tolazoline pretreatment for each dog, the difference was not significant.

Table 1
Heart rate responses and time course parameters to 10 min TI administration of KM-13

Parameter/pretreatment	Dog 1	Dog 2	Dog 3	Dog 4	$X \pm$ SE
Peak rate change (beats/min)					
Saline	83	72	77	56	72 ± 5
Tolazoline	108	84	92	69	88.3 ± 7
Latency (min)					
Saline	4.2	6.5	3.9	7.0	5.4 ± 0.8
Tolazoline	2.5	3.4	1.3	3.6	2.7 ± 0.5 [a]
Time to peak (min)					
Saline	15.5	22	24.5	31.5	23.8 ± 3.3
Tolazoline	11	14.5	18	17	15.1 ± 1.5 [a]
$T_{1/2}$ (min)					
Saline	67	92	104	119	96 ± 11
Tolazoline	36	55	47	65	51 ± 6 [a]

Peak rate change: difference in basal and maximum attained heart rate after current on; latency: time to measurable changes after current on; time to peak: time to peak response after current on; $T_{1/2}$: time from peak response to halfway back to value at baseline (time 0).

[a] Indicates values different from those after saline pretreatment (paired Student's t-test $p < 0.05$).

4. Conclusions

Transdermal iontophoresis is an effective means of delivering sympathomimetic amines into the systemic circulation. Using KM-13 in aqueous medium, effective plasma levels and cardiovascular responses were obtained at current levels which did no damage to the skin beneath the electrodes. The lack of competing ions in the working electrode (anode) is important because it allows efficient use of the current for transdermal transfer of KM-13 (Sanderson et al., 1987).

The pharmacokinetic profile of this delivery system for catecholamine is affected by the vasoconstrictor action of the drug. This results in a containment (repository) of catecholamine in the area of application and a protracted release of agent into the systemic circulation. Treatment with tolazoline, the α-adrenergic receptor antagonist, blocks the vasoconstriction and provides a more rapid and predictable effect.

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