Circulatory Effects of Salicylates

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Sodium salicylate consistently produces a prompt increase in heart contractile force when injected in anesthetized dogs in doses of 100 mg./Kg. intravenously. The increase in force is about 30 per cent and declines to control levels in 15 to 20 min. This effect is not considered of important therapeutic significance. Total doses of about 400 mg./Kg. consistently produce marked hyperpyrexia which closely resembles that of dinitrophenol and applied external heat in its circulatory characteristics; conspicuous features are extreme tachycardia, depressed S-T segment, moderate increase in heart force, and aortic pulse contours which indicate reduced stroke volume and vasodilation.

Salicylates were considered to have a direct stimulant action on cardiac muscle in recent circulatory studies reported by Tenney and Miller. Necessarily, such a characteristic could be highly significant in routine therapy of conditions such as acute rheumatic fever as well as in the relatively frequent occurrence of salicylate toxicity from therapeutic or accidental overdosage. The experiments now to be reported were intended to measure the action of salicylates on heart contractile force by more direct methods than those of Tenney and Miller, which were based on observed increases in cardiac output without important changes in heart rate and systemic arterial pressure. The measurements of the present report were obtained by means of a strain gage arch stitched to the right ventricle. These measurements, obtained in dogs under pentobarbital anesthesia with mechanical respiration, were recorded simultaneously with arterial or aortic pressures and electrocardiograms.

METHODS

Experiments were conducted in 21 mongrel dogs under anesthesia with about 30 mg./Kg. of sodium pentobarbital intravenously. After institution of interrupted positive pressure respiration, the thorax was opened in the midline and a strain gage arch was stitched to the anterior aspect of the right ventricle. This pick-up device has been described previously and the ability of such measurements to represent the intrinsic contractile state of the entire ventricular mass has been demonstrated by Cotten and associates. Femoral arterial pressures were recorded from a polyethylene catheter attached to a Statham Model P23A or P23AA pressure transducer and drugs were administered through a similar catheter in the femoral vein. In some cases, aortic pressures were recorded from a lead tube inserted through the left common carotid. The electrocardiogram (lead II) was taken from needle electrodes in the skin; in some cases unipolar leads were recorded. Analysers, amplifiers and oscillographs were those of the Brush Electronic Company (BL-320 and BL-202) or those of the Sanborn Company with carrier and electrocardiogram preamplifiers. Temperatures were measured in the descending colon with a mercury bulb thermometer.

RESULTS

The typical experiments illustrated in figures 1 and 2 demonstrate most of the essential findings. Single injections of sodium salicylate of 100 mg./Kg. consistently produced prompt increments of heart force of about 30 per cent, reaching a peak in about 2 min. and returning to control levels in 15 to 20 min. There were corresponding increments in mean arterial and pulse pressures, with little change in electrocardiogram recordings. The responses could be repeated at intervals although some diminution in the response usually occurred by about the fourth injection. In the experiment of figure 2, approximately equal responses of about a 30 per cent increase in contractile force were
Response to initial injection of sodium salicylate, 100 mg./Kg., intravenously in 30 sec. Open chest dog preparation with bilateral cervical vagosympathectomy. Femoral arterial pressure in mm. Hg and contractile force recordings from strain gage arch on right ventricle. Fast speed tracing 10 mm./sec.; slow speed 0.25 mm./sec.; heavy vertical lines, 0.5 sec. intervals for fast speed and 20 sec. intervals for slow speed.

obtained at 0, 23 and 40 min.; while a fourth injection at 57 min. produced a response of only about 12 per cent. Depending on the speed of these injections, there was sometimes an initial moderate, brief depression of contractile force and arterial pressure.

Following 3 to 4 such injections there was consistent development of progressive hyperthermia. This was always accompanied by development of external respiratory movements independent of the mechanical respiration. In this experiment, respiratory movements began at about 180 min. and shortly afterward became conspicuous. In some cases, rigor of skeletal muscle developed by the end of the experiment. The circulatory changes characteristically included a progressive increase in heart rate reaching levels as high as 300 beats/min. during the hyperthermic crisis which would then be followed by a rapid decline of rate to cardiac arrest. Arterial pressures and heart force were commonly variable during the development of hyperthermia but consistently rose during the hyperthermic crisis to reach levels at or above the original controls. The most characteristic change occurred in aortic pulse contours, the pulse pressure being significantly increased, with a conspicuously sharp ascending limb. The periods of maximal and total ejection were reduced by 50 per cent or more. Contour of the contractile force recordings also exhibited sharper rates of ascent and descent. On some occasions in other experiments there was a distinct notching and change of slope in the ascending limb of the contractile force contour which occurred at a relatively higher position as hyperthermia developed. Cotten and Bay have shown that this notching and change of slope is more characteristic of the left ventricle and corresponds to the transition from the period of isometric contraction to the period of ejection. Accordingly, the change observed in the present experiments corresponds to the development of progressively shorter periods of ejection time.

Late changes in the electrocardiogram included conspicuous S-T segment depression, A-V nodal rhythms and cardiac arrest. The S-T segment depression usually included a characteristic W shaped notching.

The prompt response to injections of salicylate illustrated in figure 1 is typical of 44 injections in 14 experiments. Most doses were 100 mg./Kg. but a few injections of 200 mg./Kg. were given without proportionately increased effects. In 7 other experiments, the salicylate was given by infusion in amounts ranging from 250 to 800 mg./Kg. over periods of about 30 min. In most instances, infusion was associated with an increase in contractile force occurring at some time during the infusion or shortly afterward. On the other hand, depression also occurred frequently and the results were generally variable. The larger doses were usually directly depressant and were followed in a short time by progressive decrease of heart force and rate with, finally, cardiac arrest.

Sympathetic block was produced in 3 animals by massive epidural infusion of procaine. In these experiments the typical positive inotropic responses to sodium salicylate were obtained. Similarly in 5 experiments with bilateral cervical vagosympathectomy, the acute responses to sodium salicylate were essentially the same as in the experiments with intact vagi. Vagotomy had no influence on the subsequent development of hyperthermia. Sympathetic block, on the
FIG. 2. Progressive effects of sodium salicylate (400 mg./Kg. intravenously in 4 installments; 100 mg./Kg. at arrows). Upper tracing, contractile force recorded from strain gage arch stitched to right ventricle; middle tracing, aortic pressure; lower tracing, electrocardiogram; heavy vertical lines, 0.2 sec. intervals. Aortic pressure calibration in mm. Hg; at 277 min., the zero baseline was shifted upward by 15 mm. (50 mm. Hg). Temperatures in the descending colon are indicated below the pressure tracing.

ther hand, conspicuously delayed the development of hyperthermia, an effect apparently due in large part to the increased heat dissipation associated with vasodilation.

DISCUSSION

These experiments have essentially confirmed the conclusion of Tenney and Miller that salicylates promptly produce a distinct and measurable increase in myocardial contractility. The effect, however, is very moderate if compared with typical stimulant drugs such as digitalis, sympathomimetic amines, xanthines, calcium or barium. Additionally the effect is of relatively short duration even when the drug is given in doses above the usual therapeutic range. Accordingly, there is little reason to consider that this may be taken as an indication that usual doses of salicylates probably do not seriously depress myocardial contractility.

The later hyperthermic effects of sodium salicylate in total doses of about 400 mg./Kg. have special interest in terms of salicylate toxicity. Hyperpyrexia is a very common feature of this syndrome and signs of circulatory failure have been recognized in fatal cases. The present experiments demonstrate that the circulatory changes during the calorigenic response of salicylates is virtually identical with that described for dinitrophenol and externally applied heat. Compared with dinitrophenol, larger doses are required with salicylates, and there is, with salicylates, a somewhat slower development of effects, a somewhat lesser increment in heart contractile force and a somewhat lower average final temperature.
Salicylate hyperpyrexia in dogs was described by McGuigan and Higgins and the closely similar action of salicylates and dinitrophenol on isolated tissues has been the subject of several recent studies. The present report establishes the identity of certain circulatory effects during hyperpyrexia not previously recognized.

**Summary**

Sodium salicylate in doses of 100 mg./Kg. injected intravenously in dogs produces a consistent but moderate and brief increase in heart contractile force. The force is increased by about 30 per cent and recovers to control levels in 15 to 20 min. The response is usually diminished by about the fourth successive injection.

Total doses of salicylates of about 400 mg./Kg. consistently produce hyperpyrexia, the circulatory features of which are virtually identical with those which have been previously described for dinitrophenol and externally applied heat.

**SUMMARIO IN INTERLINGUA**

Salicylato de natrium, administrate intra-venosemente in canes in doses de 100 mg per kg de peso corporee, produce regular ben que moderate e breve augmentos del fortia de contraction del corde. Il se tracta de augmentos de circa 30 pro cento, e le nivello de controlo es restablite in 15 a 20 minutas. Le responsa declina usualmente post circa le quarte injection successive.

Doses total de salicylates de circa 400 mg per kg de peso corporee resulta uniformemente in le production de hyperpyrexia. Le aspectos circulatori di illo es virtualmente identic con lo que ha previemente essite descripte pro dinitrophenol e applicationes externe de calor.

**REFERENCES**

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Circ Res. 1958;6:155-158
doi: 10.1161/01.RES.6.2.155

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