The Heart Rate Response to Atropine in Uremic Patients, Obese Subjects Before and During Fasting, and Patients with Other Chronic Illnesses[1] (36150)

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Impaired renal function is known to cause abnormal excretion and metabolism of some drugs. One may therefore expect to see abnormal responses to usual doses of these drugs in uremic patients. The sensitivity to drugs in renal insufficiency has not been studied extensively. Yet abnormal sensitivity could produce unanticipated drug responses just as abnormal drug elimination can. The demonstration of abnormal atropine response in Down's syndrome by Harris and Goodman (1) has prompted us to carry out a similar study in adult volunteers with uremia and other chronic illnesses.

Materials and Methods. Four groups of volunteers: 8 uremic patients, 7 patients chronically ill with either cirrhosis or pancreatitis but without uremia, 8 obese patients tested before and during the acidosis of starvation, and 7 healthy medical students and hospital staff were studied in the postabsorptive state. The age ranges for the four groups were: healthy volunteers 22–37, obese 26–48, chronically ill 18–60, uremic 30–62. The obese group consisted of 6 females whose weight ranged from 75 to 157 kg and 2 males whose weights were 100 and 116 kg. They were hospitalized for starvation for weight reduction. The patients' medications were stopped for 3 days prior to the study whenever possible. No one was receiving digitalis or any drug with chronotropic action.

For the atropine test, each patient was supine, connected to an electrocardiograph for monitoring heart rate (lead II), and had a slow infusion of saline or glucose in water running through an indwelling venous catheter in an arm vein. Following a waiting period, during which time the heart rate became stable, a placebo (normal saline) was injected into the intravenous tubing and no change in heart rate occurred. This was followed every 3 min by an injection of 0.24 mg of atropine into the intravenous tubing until a total of 0.96 to 1.20 mg of atropine had been given. The heart rate was measured by counts of the QRS complexes in each consecutive 1-min segment of a continuous electrocardiogram. The heart rate following the placebo was considered the control value and this was subtracted from the average heart rate during the second and third minutes after injection. This technique is identical to that used by Harris and Goodman (1). Heart rate changes were analyzed by Students' *t* test for group comparisons comparing each group to the healthy volunteers except for the obese group during starvation, which was compared to the obese group prior to starvation. Presence or absence of initial bradycardia was analyzed by the chi-square method. The starvation regimen was identical to that previously reported from our laboratory (2) and the atropine dose–response study was done on days 7 to 10 of starvation in the obese patients.

Results. Mean initial heart rates (±SD) were 65 ± 8 for the healthy volunteers, 74 ± 7 for the obese before and 78 ± 11 for the obese during starvation, 85 ± 17 for the uremic patients, and 74 ± 17 for the chronically ill nonuremic patients. The initial heart

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TABLE I. Initial Heart Rate (± 1 SD) and Maximum Increase in Heart Rate (change in heart rate after fourth dose of atropine).

	Normal	Chronically ill	Obese		Uremic
			Before fasting	During	
Initial heart rate	65 ± 8	74 ± 17	74 ± 7	78 ± 11	85 ± 17 [a]
Maximum increase	25 ± 6	27 ± 11	23 ± 13	25 ± 9	12 ± 6 [b]

[a] Compared to normal group: $p < .02$; [b] $p < .001$.

rates of the chronically ill, and uremic patients were not significantly different from each other but the differences between the uremic and healthy volunteers was significant ($p < .02$) (Table I).

Bradycardia, following the first dose of atropine, occurred in 6 of 7 healthy volunteers, 6 of 8 obese patients before starvation and 8 of 8 during starvation, 3 of 7 chronically ill, and 1 of 7 patients with uremia ($p < .05$).

If only the white subjects are considered, 6 of 6 healthy volunteers had initial bradycardia while none of 4 uremics had bradycardia ($p < .02$). Two of 3 chronically ill white subjects had initial bradycardia.

The mean dose–response curves for the healthy subjects, the chronically ill, and the uremic subjects are presented in Fig. 1. The uremic patients show significantly less cardiac acceleration in response to atropine (Table I). One patient (a black man) was studied during uremia of acute renal failure due to bichloride of mercury poisoning and following his recovery; his heart rate response to atropine was small during uremia and normal after his recovery (Fig. 2). While the chronically ill may have a decreased incidence of bradycardia following small amounts of atropine, their cardioaccelerator response to larger amounts seems normal. The dose–response curves of the normal volunteers and the obese subjects before starvation is shown in Fig. 3. Although a slight difference appears at the higher dose levels, when these parameters are plotted as dose per subject and dose per square meter of body surface (3), there is no difference. In addition, as shown in Fig. 4, the normal dose–response curve in the obese subjects is not modified by 7–10 days of starvation. The differences in weights between the obese group and all the other groups is significant ($p < .01$).

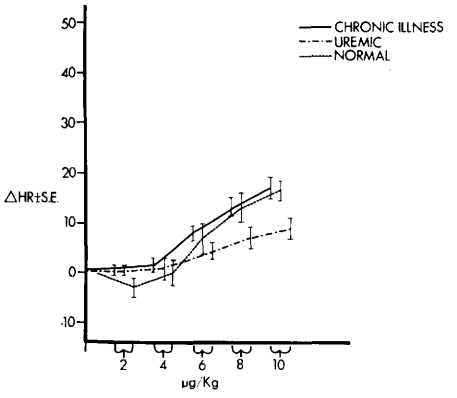

FIG. 1. Atropine dose–response curves in normal volunteers, uremic patients, and patients with other chronic illnesses: ΔHR = heart rate after cumulative atropine dose on abscissa minus initial control heart rate.

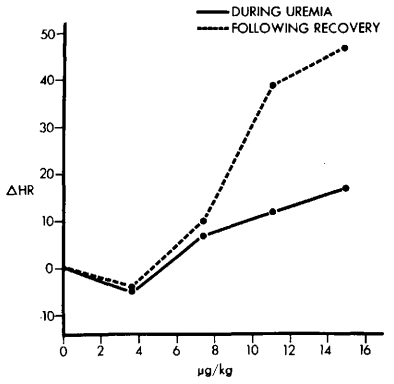

FIG. 2. Atropine dose–response curves in same subject during uremia due to acute renal failure due to self-poisoning with $HgCl_2$ and following recovery.

The BUN of the uremic subjects ranged from 124 to 180 mg/100 ml. Their hemoglobin concentrations ranged from 4.8 to 13.6 g/100 ml of blood. There was no correlation

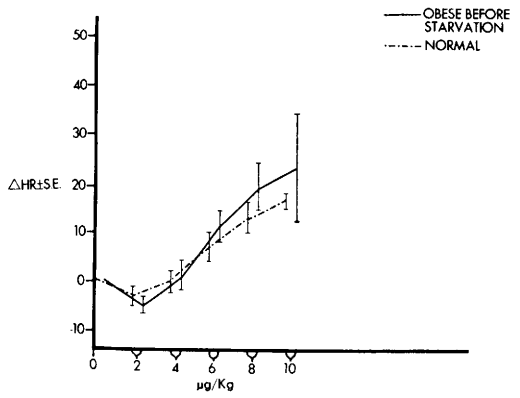

FIG. 3. Atropine dose–response curves in normal volunteers and in obese subjects before starvation.

between the BUN or hemoglobin concentration and the initial heart rate or maximum increase in heart rate in this group. There was a weak correlation between initial heart rate and maximum increase in heart rate in the uremic group ($p < .1$). For all patients taken as one group, the correlation between initial heart rate and maximum increase in heart rate was $y = -0.344\ x + 46.7$, $r = 0.51$, $p < .01$.

Discussion. The response of our normal group to atropine is the same as that of the normal subjects reported by Harris and Goodman (1) and Gravenstein and Thornby (4). The study confirms older work demonstrating an initial bradycardia in the majority of healthy people given atropine (5). Our sick patients, particularly the uremics, failed to show this consistent bradycardia. This difference was present when only white subjects were considered as well as for the total group. This type of stratification of our subjects was done because of Paskind's (5) demonstration of impaired bradycardia following atropine in Negro subjects.

In addition, the uremics also had higher control heart rates and impaired acceleration in heart rate following larger doses of atropine.

There is no nonuremic group with initial heart rates as high as the uremics. The chronically ill group however, does have a mean initial heart rate midway between the healthy volunteers and the uremic patients. There was no impairment at all in the increase in heart rate following atropine in this group. It appears that the increase in heart rate following atropine is in part inversely related to the initial heart rate and that uremic patients have a higher initial heart rate than healthy volunteers. Furthermore, denervated hearts have higher resting heart rates than innervated hearts (6, 7). Therefore, the higher resting heart rate, the lack of bradycardia following low doses, and decreased acceleration following large doses of atropine suggest that either vagal function is impaired in uremia or the cardiac pacemaker cells have decreased sensitivity to acetylcholine.

Age may contribute to the decreased response to atropine. The average age of the uremic group was 42 years. Beyond the third decade the vagal effect on the resting heart rate decreases with increasing age (8). This natural decrease in vagotonia may explain in part the higher initial heart rates in the uremic group.

Hennessy and Siemsen (20) found impaired functioning of sweat glands in uremic patients. Goldenberger *et al.* (9) found abnormal heart rate or blood pressure responses in some uremic patients following the Valsalva maneuver and abnormal sweating responses to pilocarpine given by iontophoresis. Both groups suggested that this was due to impaired autonomic nervous system function in uremia. Our results are in agreement with these conclusions. Tyler (19) has recently reviewed neurologic disorders in renal failure but did not mention autonomic neuropathy.

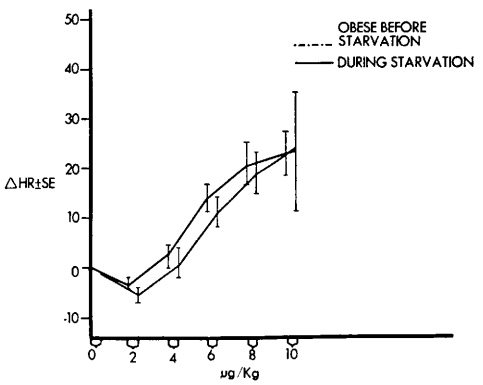

FIG. 4. Atropine dose–response curves in obese subjects before and during a period of fasting.

Nevertheless, it may exist.

The temperate environment (av room temp, 70°F; and relative humidity, 50%) in which the study was done probably did not influence the response to atropine. It has been shown that a hot dry climate can contribute to circulatory collapse when atropine is given to the unacclimatized subject (10).

Fasting with ketoacidosis did not alter the atropine dose–response curve in our obese patients. Therefore, acidosis alone cannot be the cause of the abnormal atropine dose–response curve in the uremic patients.

Abnormal drug responses have been seen in uremic patients and usually attributed to impaired drug excretion. Abnormal drug metabolism (11) can also occur in uremia and the present study shows abnormal drug sensitivity in uremic patients. Uremic patients may have increased sensitivity to drugs such as barbiturates (12) or cephalothin (13), or decreased sensitivity to such drugs as insulin (14) or sodium urate crystals (15). *In vitro* evidence for decreased tissue sensitivity has been demonstrated by the suppression of interferon (16) response in uremic lymphocytes and by depression of reactivity of lymphocytes to phytohemagglutinin by uremic sera (17).

Normally atropine is partially metabolized and partially excreted unchanged by the kidney (18). Cumulation should occur in the uremic. The flat dose–response curves in the uremic patients would not be expected to result from either impaired excretion or impaired metabolism. While accelerated metabolism of atropine in uremic patients is theoretically possible, we think it unlikely.

Summary. Atropine sensitivity was tested in uremic patients by measuring the heart rate response to four 0.24 mg doses given intravenously at 3-min intervals following a control period. Four groups were studied: 7 healthy volunteers, 8 obese patients before and during starvation, 8 uremics, and 7 chronically ill nonuremic patients. The uremic patients had a flat dose–response curve. Their lack of bradycardia following low dosage and decreased acceleration following large dosage suggest that either vagal function is impaired or that their pacemaker cells have decreased sensitivity to acetylcholine.

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