Toxicity of Penicillin for the Syrian Hamster. (22221)

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Observation of the unique toxicity of penicillin to guinea pigs as compared to mice and rabbits was first made by Hamre *et al.*(1) and has since been amply confirmed(2-8). Except for generalized state of vasodilatation, very few pathological changes have been noted to account for death of the animals. The cause of this toxic effect has been variously ascribed to:—acute necrosis involving the adrenal gland, particularly of the cortex (4); allergy to penicillin(6); possible deficiency state with effects very similar to those produced by X-rays(7); and finally to change induced by penicillin in predominantly Gram positive intestinal flora of guinea pigs thereby permitting overgrowth of non-sensitive Gram negative bacteria and production and resorption of toxins of the latter(8).

Existence of this unusual sensitivity to penicillin has not been reported in other animals. During experiments on Syrian hamsters treated with penicillin, it was first noticed that mortality rate of treated group consistently exceeded that of untreated controls. Because of observations in guinea pigs and of their widespread use in research, we investigated the possible toxic effect of penicillin upon hamsters.

Methods. Syrian hamsters, of either sex, weighing 50-60 g were employed in groups of 10. A single injection of crystalline penicillin G potassium (Bristol) was administered to each hamster in dose and route indicated in Table I. Volume injected subcutaneously was 0.25 ml and intraperitoneally 1 ml. All animals were kept on normal diet and observed 21 days. Symptoms were noted, total mortality and days of death were recorded for each group. Because of reported resistance of mice and susceptibility of guinea pigs to penicillin, these were included for comparison. Two groups of 10 Swiss mice, weighing 15-20 g and 2 groups of 10 guinea pigs, weighing approximately 200 g received 100000 units of crystalline penicillin G potassium. One group of each species was injected subcutaneously and the other intraperitoneally in 0.25 ml and 1 ml amounts, respectively. In addition, groups of each species received the same volume of physiological saline by same route as those receiving penicillin.

TABLE I. Toxicity to Syrian Hamster and Mortality Time of One Injection of Variable Doses of Crystalline Penicillin G Potassium Administered Subcutaneously and Intraperitoneally.

	Subcutaneous		Intraperitoneal	
Penicillin (units)	Mortality	Days of death (No.–day)	Mortality	Days of death (No.–day)
×1000				
1	1/10*	1–7	0/10	—
5	"	1–3	2/10	1–2; 1–3
10	3/10	1–3; 2–4	4/10	2–2; 2–3
25	"	3–3	5/10	3–3; 2–4
50	5/10	1–3; 2–4; 1–8; 1–12	9/10	3–3; 4–4; 1–5; 1–6
100	9/10	4–4; 4–5; 1–7	10/10	3–4; 6–5; 1–6

* Numerator = No. died. Denominator = Total No. animals injected.

Results. No deaths were observed in control animals in the 3 animal species under consideration that received physiological saline either subcutaneously or intraperitoneally. From Table I, it may be noted that a single injection of penicillin starting with 1000 units subcutaneously and 5000 units intraperitoneally is toxic for some hamsters. Increasing the dose by either route results in progressively higher mortality until a 90-100% rate is observed with 100000 units. Intraperitoneal administration proved more toxic than did subcutaneous, as evidenced by consistently higher mortality rate in animals receiving the antibiotic by former route. The peak mortality period for varying doses of penicillin is also illustrated in Table I. No deaths occur on 1st day, only 3 out of 52 deaths are found on 2nd day and vast majority of deaths takes place on 3rd, 4th and 5th days following injection. Few deaths supervene after this time. It is of interest to

TABLE II. Comparative Susceptibility of Swiss Mice, Guinea Pigs and Syrian Hamsters to One Injection of 100000 Units of Crystalline Penicillin G Potassium.

Animal	Subcutaneous		Intraperitoneal	
	Mortality	Days of death (No.–day)	Mortality	Days of death (No.–day)
Mice	0/10	—	0/10	—
Guinea pigs	10/10	1–3; 3–4; 3–5; 2–6; 1–7	8/10	1–3; 2–4; 4–6; 1–7
Hamsters	9/10	4–4; 4–5; 1–7	10/10	3–4; 6–5; 1–6

note that increased dosage of penicillin produces higher mortality rate but no shortening of survival time. On the contrary, with higher doses, peak mortality is delayed a day or two rather than accelerated as compared with lower amounts. Thus peak mortality day with 25000 units or less is the 3rd, with 50000 units, the 4th, and with 100000 units the 5th day. The picture presented by the hamsters was similar to that previously described for guinea pigs. Food and water intake was diminished, hair became ruffled, animals were lethargic and huddled together in a shrunken posture.

By contrast, as seen in Table II, Swiss mice weighing only 15-20 g readily tolerate a single injection of 100000 units of penicillin administered either subcutaneously or intraperitoneally. They remain alive and active throughout the 21-day observation period. On the other hand, the same dose of antibiotic causes death in 80-100% of guinea pigs and in 90-100% of hamsters similarly treated, depending upon route of administration. The mortality pattern in hamsters closely parallels that in guinea pigs as toxicity of penicillin for both is of the delayed type. Thus in both species no deaths are noted before the 3rd day or after 7th day following injection.

In the light of our findings, reevaluation of experimental data concerned with Syrian hamsters either treated with penicillin or injected with material sterilized with penicillin would seem to be indicated. Although amounts less than that reported in this study as capable of producing toxic effects in hamsters might have been employed, the cumulative effect of multiple small injections might well produce the same result and render observed experimental data inaccurate.

Summary. A single injection of crystalline penicillin G potassium administered subcutaneously or intraperitoneally is toxic for hamsters in proportion to amount administered. Toxicity is of the delayed type, the vast majority of deaths occurring on 3rd, 4th and 5th days following injection. This parallels the reported experience with guinea pigs and is in contrast to Swiss mice who easily tolerate very large doses of this antibiotic. In the light of these findings, reevaluation of experimental data concerned with Syrian hamsters either treated with or injected with material sterilized with penicillin would seem to be indicated.

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