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Nickel Acetate-Induced Mortality in Mice of Different Ages

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Nickel has been shown to be related to a wide variety of pathophysiological conditions (Harrison 1979; Sunderman 1977), spanning a broad spectrum of events from gamete formation to the attainment of sexual maturity (Dixon and Collins 1979). These effects are variable depending upon such factors as recipient species, anion component of the nickel compound (Hopfer et al. 1976), solubility property of the salt, and route of administration (English et al. 1981). There is, however, little, if any data available in regard to nickel toxicity in animals of different ages and sex. The purpose of this study was to determine the time course and extent of nickel-induced lethality in juvenile male and female mice and to compare juvenile responses to those in adult mice of both sexes.

MATERIALS AND METHODS

Mice of the ICR strain were used throughout this study with standard rodent diet and tap water freely available. Ages of adult animals were approximately 9 and 15 wk and 3 wk for juveniles. At the time of treatment mean body weights for adult males and females were 29 and 23 g with ranges of 26-32 g and 19-29 g, respectively. Juvenile mice had a mean weight (and range) of 18 g (17-20 g) for males and 16 g (13-17 g) for females. Nickel acetate, $NiAc_2$ (Alfa Research Chemicals and Materials, Danvers, MA, USA), was administered by a single i.p. injection. Stock solution was prepared the day of injection with serial dilutions made and used for the injection series. Treatment was based upon mg $NiAc_2$/kg body weight, and adjusted so that the injection volume was 0.1 ml $NiAc_2$/10 g body weight. Control mice of comparable age and sex were injected with an equivalent volume of isotonic saline. Ten animals comprised each injection subgroup. Following injections (day 0) mortality ratios, i.e., number dead compared to the initial number treated, were recorded for each subgroup. From these ratios the median lethal dosages (LD_{50}) and their 95% confidence intervals were calculated for days 1, 3, and 5 using the method of moving averages as described by Thompson and Weil (1952). The LD_{50} values were used as indices of vulnerability to $NiAc_2$,

whereby the lower the mg/kg value, the more susceptible the group to $NiAc_2$. Split dose studies were conducted using 3-wk and 15-wk old mice. Animals were injected with a lethal dose of $NiAc_2$ that was divided into two equal parts. The two injections were separated temporally by 1/2, 1, or 2 days. The juvenile and adult male and female groups received a total dosage of 133 and 81 mg/kg, respectively.

RESULTS AND DISCUSSION

Table 1 shows the mortality responses of 3-, 9-, and 15-week old mice following a single $NiAc_2$ injection. The time at which group lethality is maximum does not appear to vary markedly between age and/sex groups. Even though observations were made through day 14 post-$NiAc_2$, no deaths within any group were noted after day 5 except for one further death (day 9) in the 9-wk old female group. As soon as possible following death, autopsies were conducted. No internal hemorrhage, congestion, or necrosis were observed in the peritoneal cavity of $NiAc_2$- or saline-injected mice. In no instance were any deaths observed in the control group within the two-week period of observation.

Mortality to $NiAc_2$ varied dramatically between the juvenile groups and the adult ones. On day 5 the 9-wk and 15-wk old adult males' LD_{50} were about 56 and 44 percent of the juvenile male group. There is, however, a suggestion that the 9-wk old male may be somewhat more $NiAc_2$-resistant than its 15-wk old counter part. This observation has been confirmed by a number of comparable investigations in this laboratory. Similar differences in LD_{50} were noted for adult females compared to juvenile females. The LD_{50} values calculated on day 5 for 9-wk and 15-wk old females were 56 and 50 percent of the 3-wk old female group's LD_{50}. In contrast to other investigations using lead (Kostial et al. 1974; Hogan 1980), data in this study demonstrate a lack of difference in mortality between the sexes to nickel irrespective of age. Similar results for all observations given above have been confirmed from experiments with ICR mice of the same age but varying from those described above in that two different injection series (15, 30, 60, and 120 mg/kg and 30, 44, 66, and 100 mg/kg) were employed. The corresponding LD_{50} values that were obtained were quite comparable to those given in Table 1 for a particular age and sex subgroup.

Table 2 illustrates the mortality responses of 3-wk and 15-wk old mice to split dose treatment of $NiAc_2$. The younger animals appear to be more tolerable to treatments than adults when the second dosage is separated from the first by one or two days. Twelve-hour separation does not appear to have any effect on mortality as indicated by one-hundred percent deaths in all groups by day 3. Without exception, there were no deaths observed between the first and second injections.

Lethality is directly related to the age of the $NiAc_2$-treated animal. Considering the LD_{50} values as sensitivity indices, the

Table 1. Time course of lethality for mice of three age groups following a single injection of nickel acetate.

Group/ Age	Day	Mortality Ratio[a]				LD_{50} (mg/kg)	95% Confidence Interval (mg/kg)
3-Week[b]							
Male	1	0/10	0/10	8/10	10/10	92	85-100
	3	0/10	0/10	9/10	10/10	89	84-95
	5	0/10	0/10	9/10	10/10	89	84-95
Female	1	0/10	0/10	5/10	10/10	100	91-111
	3	0/10	0/10	6/10	10/10	97	89-107
	5	0/10	0/10	6/10	10/10	97	89-107
9-Week[c]							
Male	1	0/10	0/10	5/10	9/10	—[d]	———
	3	0/10	0/10	6/10	10/10	52	45-60
	5	0/10	0/10	7/10	10/10	50	43-56
Female	1	0/10	0/10	0/10	6/10	—[d]	———
	3	0/10	0/10	6/10	9/10	54	44-66
	5	0/10	0/10	6/10	9/10	54	44-66
14-Week[c]							
Male	1	0/10	0/10	6/10	10/10	52	45-60
	3	0/10	1/10	9/10	10/10	44	39-49
	5	0/10	3/10	10/10	10/10	39	35-42
Female	1	0/10	0/10	0/10	10/10	—[d]	———
	3	0/10	0/10	5/10	10/10	54	47-62
	5	0/10	0/10	8/10	10/10	48	43-53

[a]Numerator = number dead on a given day and denominator = initial number of mice injected on day 0.

[b]Injection series = 56, 75, 100, and 133 mg/kg.

[c]Injection series = 24, 36, 54, and 81 mg/kg.

[d]Mortality ratio not given in tables for LD_{50} determination.

older mice were approximately two times more sensitive than the 3-wk old group. It is possible that accumulation of the metal is responsible for lethality and that the amount of metal in tissue is related to toxicity. Sunderman and coworkers (1978) have demonstrated that nickel is concentrated in a number of critical targets such as kidney, lung, heart, and liver. Jasmin and Riopelle (1976) have shown that the kidney is highly susceptible to nickel. Perhaps, adult mice are not capable of as rapid a $NiAc_2$ renal clearance as juveniles, or the age variation to nickel toxicity could be due to differences in the rate/extent of repair of nickel-induced lesions. Data from the split dose studies may indicate this. Neither juvenile nor adult survived

the lethal split dose separated by one-half day, but it is shown that the juveniles exhibit lower mortality percentages than adults when the split lethal dose is separated by one or two days. Whatever mechanism(s) that accounts for the different responses to nickel toxicity, it is clear that 3-wk old mice are less sensitive to nickel than those that are 9-wk and 15-wk old.

Table 2. Mortality in ICR mice receiving a split dosage treatment of nickel acetate.

Group	(Number Treated)	Separation Interval (Days) between Doses[a]	Percent Mortality[b] on Days[c] 3	4	5	6	7
Juvenile							
Male	(16)	1/2	100	100	100	100	100
	(15)	1	27	30	33	33	33
	(15)	2	6	13	20	20	20
Female	(20)	1/2	100	100	100	100	100
	(17)	1	17	29	29	29	29
	(15)	2	0	13	20	20	20
Adult							
Male	(14)	1/2	100	100	100	100	100
	(17)	1	53	53	53	70	70
	(15)	2	33	33	33	53	53
Female	(19)	1/2	100	100	100	100	100
	(15)	1	40	40	50	67	73
	(16)	2	19	25	38	38	44

[a] Juvenile dosage = 66.5 mg/kg on day 0 and 66.5 mg/kg at times indicated above. Adult dosage = 40.5 mg/kg on day 0 and 40.5 mg/kg at times indicated above.

[b] $(1-N/N_o) \times 100$. N = number surviving at an interval, N_o = original number of animals treated on day 0.

[c] Days represent times following the second $Ni(Ac)_2$ injection.

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