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SHORT LIVED NUCLIDES IN THE FOOD CHAIN AND MAN

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PROPHYLACTIC REDUCTION OF THYROIDAL IRRADIATION
FROM ^{131}I BY THE USE OF POTASSIUM IODIDE*

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Release of radioactive iodine to the environment is one of the potential hazards arising out of certain applications of nuclear energy. Thus, ^{131}I was widely present in the environment in recent years as a consequence of nuclear weapons testing, resulting in low level contamination of milk supplies. Human exposure is also possible as a result of the industrial, medical, or research use of ^{131}I , and could be particularly significant following reactor or fuel processing plant accidents. Indeed, accidental exposures have been reported (1,2), and the sequela in one instance of massive overexposure has recently been shown to include thyroid nodules, hypothyroidism, and short stature (3).

Ingestion is probably the main route of human radioiodine exposure, but inhalation may be important in some instances. Of the several radioactive isotopes of iodine, ^{131}I is the focus of concern because of its relatively long half-life and energetic beta and gamma emissions. Other iodine isotopes are of lesser importance except promptly after low level nuclear reactions.

* From the departments of medicine and environmental medicine.

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Atmospheric radioiodine is deposited on foliage and because of the large area grazed by cows, the physiology of lactation, and the rapidity with which dairy products reach the consumer, the principle route for human absorption is cows' milk. In the case of other food or water moving more slowly to the consumer, appreciable decay of radioactivity usually occurs. The hazard of ^{131}I exposure after atmospheric release is particularly relevant to children because of their large milk consumption and small thyroid glands but the potential risk to adults involved in localized accidents or "spills" may also be substantial (1).

Iodine is rapidly absorbed from the small intestine or lungs and to some degree from the skin, and is distributed to the extra-cellular fluid from which it is sequestered by the thyroid, synthesized into thyroglobulin, and secreted as thyroxine. Thyroidal iodine uptake is depressed when serum iodide concentration is elevated and therefore inorganic ^{127}I administration prevents radioiodine accumulation by the gland.

The object of our study was to investigate the efficacy of KI in suppressing thyroidal ^{131}I uptake as a means of reducing the risk of thyroid damage due to single massive exposures to this isotope. Since exposure might be unavoidable in the event of an accident, it is desirable to have a prophylactic procedure to minimize or prevent absorption of radioiodine by the thyroid. In contrast, the relatively moderate repeated exposure that might occur among individuals working with radioiodine in hospitals or research laboratories can be controlled by proper design of equipment and working habits.

There have been several investigations of blockade of thyroidal radioiodine uptake but little specific information is available regarding the dose of drug, rapidity of onset of effect, or duration of effectiveness (4,5,6). We extend the previous observations to a larger number of subjects, confirm the efficiency of 100-200 mg KI in promptly inhibiting thyroidal concentrating ability, show that a single dose of KI is progressively less effective as a blocking agent after 1 or 2 days, and demonstrate that the extent of thyroidal suppression may be predicted from serum inorganic iodide measurements.

Method

Thyroidal ^{131}I uptakes were measured in 62 healthy volunteers, 37 males, and 25 females, ranging in age from 21 to 72 years. A total of 110 control determinations were done in these subjects. The percent thyroidal ^{131}I accumulation was determined 24 hours after the administration of a standard dose of 1.5 mc (1.5×10^{-3} μc) carrier free [Squibb], dissolved in 10 ml of water. Studies were carried out in a low background steel room using two 3" x 3" thallium activated sodium iodide scintillation crystals placed in contact with the anterior surface of the neck, from the sternal notch to the thyroid cartilage. The details of the procedure have been reported in previous communications from this laboratory (7). This method was employed because it minimizes the irradiation dose to the subject, the infinity thyroid dose for 30% thyroidal uptake of ^{131}I being 6.8 mrem/1.5 mc.

The volunteers were examined by clinical and laboratory means including determinations of protein bound iodine*, 24 hour thyroidal ^{131}I uptake, and ^{131}I labeled triiodothyronine resin uptake. Two subjects were found to be hypothyroid and were rejected from the study; all others were euthyroid. One, using a drug, "Enovid," for contraceptive purposes had a low resin uptake, as expected, but was euthyroid and was included in the study.

The effect of KI administration on thyroidal radioiodine accumulation was investigated in 24 male and 17 female members of the above group. These subjects received doses of stable potassium iodide (^{127}I) ranging from 5-1000 mg dissolved in cherry syrup either one hour prior to, with, or at specified times following administration of the radioiodine. One or two days later, an additional dose of 1.5-5 mc of ^{131}I was administered without a further dose of KI and the 24 hour uptake was again measured to evaluate the duration of the suppressive effect.

The uptakes are not corrected for extra-thyroidal iodine because attempts to measure this component proved to be inaccurate. Since iodide other than that concentrated and organified by the thyroid is cleared by the kidney at a rate about twice that of thyroidal clearance, extra-thyroidal iodide normally accounts for a very small part of the total neck activity at the end of 24 hours (8). After blockade of thyroid uptake, however,

*PBI and free iodide measurements were made by Bio-Science Laboratories, Van Nuys, California

extra-thyroidal iodide may constitute the largest part of neck activity. Therefore, our neck measurements yield estimates of thyroid concentrations which are somewhat high particularly when uptake has been blocked and during the first few hours in unblocked subjects. This leads to conservative estimates of the efficacy of the blocking regimen.

Results

Figure 1 shows the average uptake of the 62 volunteers to have been 27.1% in 24 hours with a standard deviation of \pm 8.9%. The frequency distribution of these data is shown in the insert.

The ability of the thyroid to accumulate radioiodine is reduced by potassium iodide administered with the isotope. None of the 25 subjects receiving more than 50 mg of KI together with ^{131}I concentrated more than 1.3% of the dose and the average radioiodine percent uptake after 100 and 200 mg KI is 0.6 ± 0.5 (n=14) and 0.3 ± 0.3 (n=10) respectively, (Table 1 and Figure 2).

Figure 3 demonstrates that radioiodine accumulation ceases promptly after KI administration. Delayed institution of therapy is progressively less effective in decreasing thyroidal isotope burdens but more than 50% uptake reduction occurs even if the countermeasure is started three hours after exposure to ^{131}I has begun. The data in Table 1 suggests that 1000 mg KI may be slightly more effective than 100-200 mg in suppressing uptake if the drug is given one hour after the KI. However, these are single determinations, the variability of which are unknown, and the

differences are not great. When the delay is greater than one hour, the extent of variation of accumulation in a population prior to KI administration is large, as is seen in Figure 1. Therefore, the only meaning which can be assigned to our individual observations is that 24 hour burdens increase with delay in KI ingestion. Statements concerning relative effects of various dose levels are not warranted on the basis of these data.

Figure 4 and Table 2 demonstrate that the uptake of ^{131}I administered 48 or 72 hours after KI is less than control values and varies inversely with the amount of iodide given. One hundred milligrams or more of potassium iodide lowers ^{131}I uptake to some degree for 48 hours but the extent of inhibition is not as complete as when the drug is given with the radioiodine. Marked uptake arrest 48 hours after KI ingestion was observed only with the 1000 mg dose and even this large amount was largely ineffective in blocking thyroidal ^{131}I uptake if given 72 hours before the contaminating episode.

Toxic reactions to iodides were not encountered in this study although two subjects reported uncomfortable sensations at the angles of the jaw and headache for several hours after ingesting 1000 mg KI.

Discussion

The effect of KI on thyroidal ^{131}I accumulation was studied in healthy volunteers in order to clarify its optimal use as a countermeasure for massive radioiodine exposure, as in the case of occupational exposure following laboratory or industrial accident.

Adams and Bonnell demonstrated in two volunteers that the use of 100 mg of KI lowers the 24 hour radioiodine uptake from normal values to less than 3% of the amount ingested and Pochin and Barnaby observed arrest of subsequent thyroidal concentration in 6 subjects when 200 mg KI was administered up to 4 hours after a dose of radioiodine (4,5). Saxena, Chapman and Pryles reported gradual suppression to 5% after daily administration of 2 mg KI per square meter body surface, with 50% of the reduction taking place in the first 24 hours, and uptakes returning to or above pretreatment levels promptly after drug discontinuation (6).

Although Johnson found 50-20% reduction from normal 3-4 days after cessation of KI and disappearance of effect after 8 days, Taguchi et al. noted population heterogeneity with rebound thyroidal hyperavidity in 3 of 24 subjects (9,10).

The ^{131}I uptakes observed in this series are similar to those obtained with conventional clinical methods except that the number of observations below 20% is somewhat high. Phantom studies have suggested that this may be related to detector position and decreased counting efficiency of the lower poles of the thyroid. Since each individual served as his own control and constancy of geometry was maintained, such variation does not affect the conclusions reported here.

In one of the subjects, M.E., the initial uptake was only 13% but he was clearly euthyroid by other indicies. This may have been due to counting geometric errors for this subject. Recall that extra-thyroidal iodide is not corrected for, and that this may comprise a large part of his neck burdens after blockade. Following suppressive therapy, neck concentrations in this subject (1.2 and 1.3% after 100 and 200 mg KI) were similar to those observed in others under comparable conditions.

There is no doubt that 100-200 mg KI given at the time of exposure can largely prevent thyroidal radioiodine uptake and thereby minimize the radiation dose to the gland. Administration of the drug after exposure to ^{131}I promptly blocks further accumulation by the thyroid but previously concentrated isotope remains in the gland to be metabolized and secreted at a slow rate (11,12). The rapid inhibition of accumulation is shown in Figure 3 and the decrease in neck radioiodine activity shortly after blockade probably reflects clearance of ^{131}I from the blood by the kidneys which, unlike thyroidal clearance, is not depressed by elevated serum iodide concentrations. Figure 2 demonstrates that increasing the amount of KI above 100-200 mg does not seem to reduce concentrating ability any further or to discharge previously accumulated ^{131}I .

The blocking agent is most effective if given with or just before radioiodine exposure. The extent of suppression observed was sharply reduced when the iodide was given 48 hours before ^{131}I . Iodide is rapidly excreted by the kidney from the extra-thyroidal pool, accounting for the short duration of protection afforded by a single ingestion of KI. Therefore, in the event of prolonged radioiodine exposure daily KI

readministration is required for maintenance of suppression. The use of KI after exposure to the isotope also permits the concentration of radioiodine by the thyroid. The greater the lag in the institution of the countermeasure, the larger the isotope burden, but about 50% protection was noted even if three hours had elapsed between radioiodine ingestion and KI therapy.

It might be desirable to know the extent to which thyroïdal radioiodine uptake has been inhibited in exposed populations without performing actual uptake measurements. Our data shows that less than 1.3% uptake may be expected with serum inorganic iodide concentrations of at least 10 µg%. These levels correlate with suppression of 95% on the curve in Figure 5 and are achieved by administering at least 50 mg KI with, or 200 mg 48 hours prior to radioiodine exposure. The actual observations show that 98% \pm 3% suppression occurs after 100-200 mg KI. Since the techniques for measuring serum iodide concentrations are commonly available, such determinations may serve as a useful index of protection. However, since the ability to accumulate iodide probably reflects thyroïdal ¹²⁷I burdens rather than serum concentrations this relationship is only an indirect index of suppression. The association can be made with confidence at elevated serum concentrations and decreases as physiologic inorganic iodine levels are approached.

The actual thyroid uptakes are somewhat lower than the neck burdens reported due to our inability to correct reliably for extra-thyroidal iodine. Therefore, the suppressive effect of the countermeasure is slightly underestimated.

Toxicity to iodide was not encountered and the two subjects who experienced discomfort at the angles of the jaws when taking 1000 mg KI were not incapacitated. Since 100-200 mg KI was just as effective as 1000 mg in causing uptake blockade, and had the advantage of not eliciting undesirable side effects, the use of larger doses is unnecessary. Toxic reactions from a single dose of KI or from short term administration is most unlikely except for occasional allergic reactions which are usually mild (13).

A word might be added concerning chronic use of iodide as a counter-measure for prolonged radioiodine exposure. In this circumstance untoward reactions are uncommon but there is a small risk of hypersensitivity, goiter, Jod Basedow, hypothyroidism and ioderma. Neonatal goiter and respiratory distress developing in the offspring of mothers who took iodide is an important problem requiring caution in the prolonged use of iodides during pregnancy and iodide ingestion is unwise in people with chronic renal disease, cardiac failure and pulmonary tuberculosis (13). It is to be stressed that a single ingestion, such as used here, in the suggested dose range is largely harmless.

In view of the possible serious consequences from exposures to large amounts of ¹³¹I and the safety and effectiveness of KI in blocking thyroidal radioiodine uptake, it may be wise to provide 200 mg KI capsules in high risk areas for immediate use by adults in the event of massive exposure to radioiodine. Large supplies of the drug could be strategically located for population use at the discretion of public health authorities (14,15).

Pediatric dose considerations in this regard have been previously discussed in the literature (6). This countermeasure would supplement but not replace evacuation from a contaminated environment.

Summary

The prophylactic administration of 100-200 mg KI in anticipation of radioiodine exposure will largely prevent uptake by the thyroid gland thereby reducing the irradiation dose delivered by more than 98%. The same amount given at intervals after ^{131}I absorption is progressively less effective, but still reduces uptake to less than half after a delay of 3 hours. The suppressive effect of one dose is of short duration and daily readministration of the agent is required for prolonged protection. The extent of uptake blockade may be estimated by measuring serum inorganic iodide, and concentrations of greater than 10 μg per 100 ml correlate with marked uptake arrest. Toxicity is negligible for a single ingestion or very short term use as is required in this temporary measure for the reduction of the immediate thyroidal irradiation hazard, but the drug must be avoided by those allergic to it.

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24 Hour Thyroidal ¹³¹I Uptake Before and Specified Times (Hours)

After Single Dose KI (5-1000 mg) Administration and Resultant

Percent Reduction of Uptake

Dose KI (mg)	Time of Admin. of KI (I-131 admin. at t=0 hrs.)	Subject	24 hr. Uptake Before KI (%)	24 hr. Uptake After KI (%)	Reduction in Uptake (%)
5	0	BL	33	7.3	78
25	0	KW	41	1.4	96
	1	SR	31	7.1	77
	2	SV	18	11.3	36
	6	EL	24	9.5	60
50	0	RC	28	0.8	97
	1	BS	41	6.1	85
	2	AS	34	6.8	80
	3	IB	35	9.0	75
	4	IG	36	6.0	83
100	0	MB	17	-0.1	101
		LL	25	0.0	100
		FE	34	1.3	96
		GB	37	-0.1	100
		VK	32	0.7	98
		CC	36	0.5	99
		JC	25	1.1	96
		BC	52	1.2	98
		AC	31	0.1	100
		HD	25	0.5	98
		ME	13	1.3	91
		IE	32	0.8	97
		MEW	13	0.4	97
		AVERAGE ± SD	29 ± 11	0.6 ± 0.5	98 ± 3
	1	LS	28	3.1	89
		HB	44	2.9	93
		AVERAGE ± SD	36 ± 11	3.0 ± 0.1	91 ± 3
	2	MA	28	5.7	80
		BW	18	2.3	88
		AVERAGE ± SD	23 ± 7	4.0 ± 2.4	84 ± 6
	3	GM	17	6.8	60
200	0	AS	16	-0.8	105
		FC	18	-0.3	102
		HP	36	0.6	98
		NC	33	0.2	99
		AC	31	0.4	99
		RP	20	0.5	97
		ME	13	1.3	90
		IE	32	0.8	97
		GL	21	0.1	100
		CS	32	0.5	98
		AVERAGE ± SD	25 ± 8	0.3 ± 0.3	99 ± 4
	1	PP	26	3.1	88
	2	RM	14	3.5	74
	3	MEW	20	7.0	64
	4	DN	13	8.3	34
100	0	AG	31	0.2	99
	1	AL	31	1.1	96
	2	FP	24	7.2	70
	3	IG	36	6.0	83

TABLE 2A

Effectiveness of KI Administered 48 Hours Prior to ^{131}I Dose

Subject	Dose KI (mg)	24 hr. Uptake Before KI (%)	24 hr. Uptake After KI (%)
SR	25	31	24
SV	25	18	24
LB	50	35	6.5
HJ	50	27	16
LS	100	28	6.9
DM	200	13	4.5
BG	1000	28	1.2

TABLE 2B

Effectiveness of KI Administered 72 Hours Prior to ^{131}I Dose

Subject	Dose KI (mg)	24 hr. Uptake Before KI (%)	24 hr. Uptake After KI (%)
EL	25	24	25
IG	50	36	14
MA	100	28	20
CM	100	17	14
AL	1000	31	7.8
EP	1000	24	12

LEGEND

Figure 3

Effect of Delayed KI Administration on Thyroidal ^{131}I Uptake.

The X - - - X line represents thyroidal uptake before and KI was given. \triangle — — — \triangle line represents thyroidal uptake when 200 mg KI was given 1 hour after ^{131}I . The \triangle - - - - \triangle line represents thyroidal uptake when 200 mg KI was given 3 hours after ^{131}I .

NORMAL THYROIDAL ^{131}I UPTAKES OF VOLUNTEERS

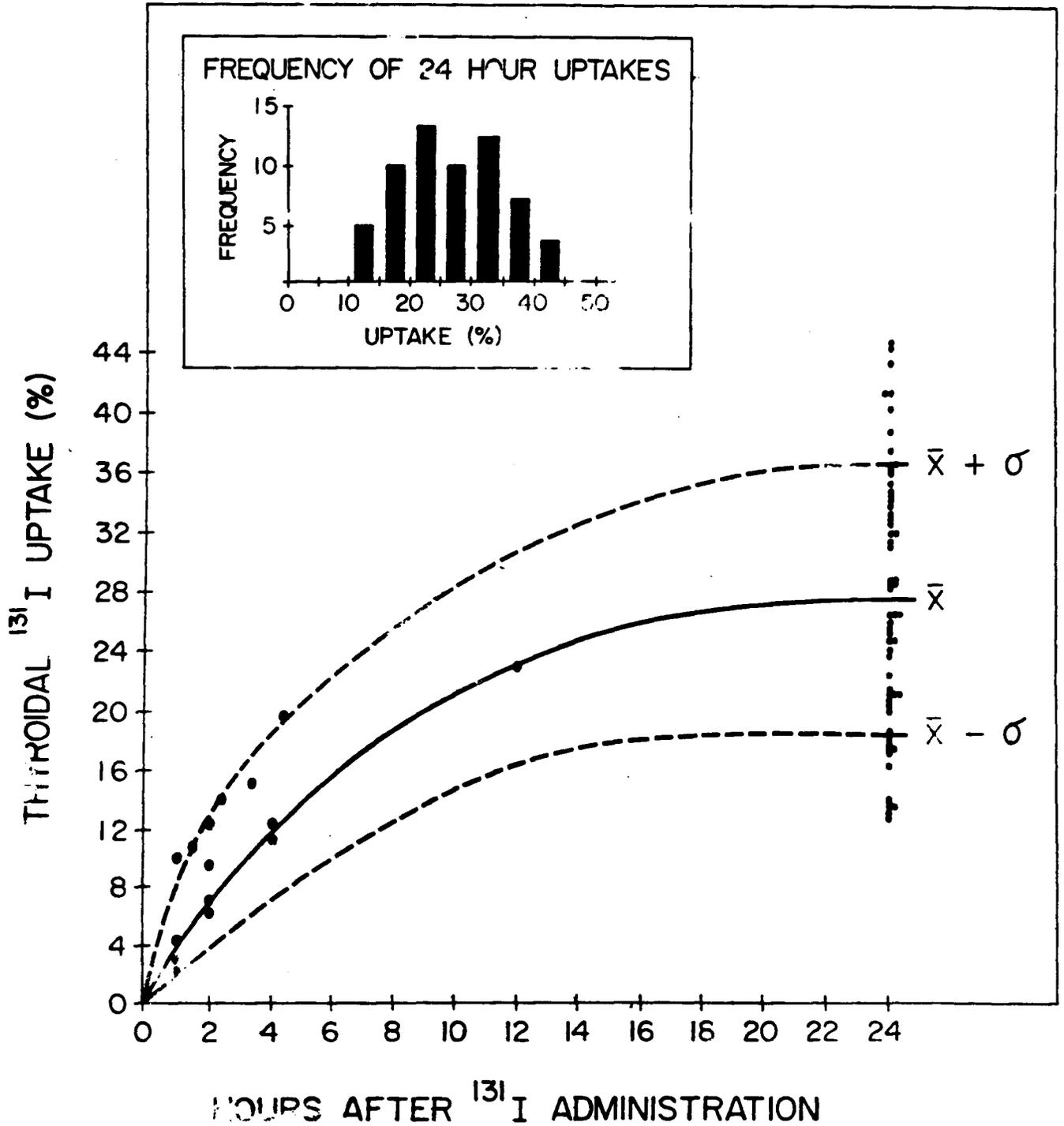


FIGURE 1

THYROIDAL ^{131}I UPTAKES - KI COADMINISTERED WITH ^{131}I

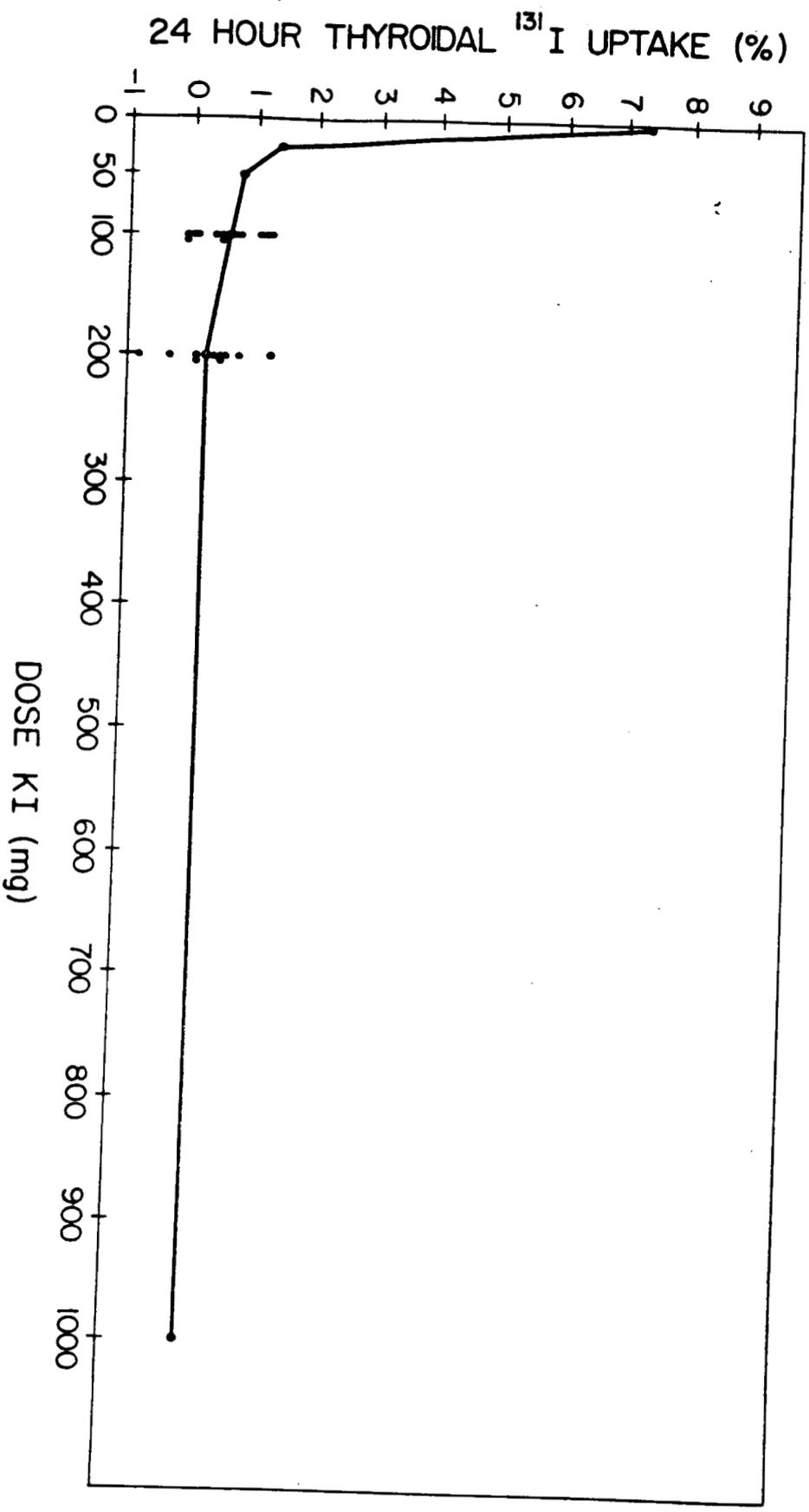


FIGURE 2

EFFECT OF DELAYED KI ADMINISTRATION ON THYROIDAL ^{131}I UPTAKE

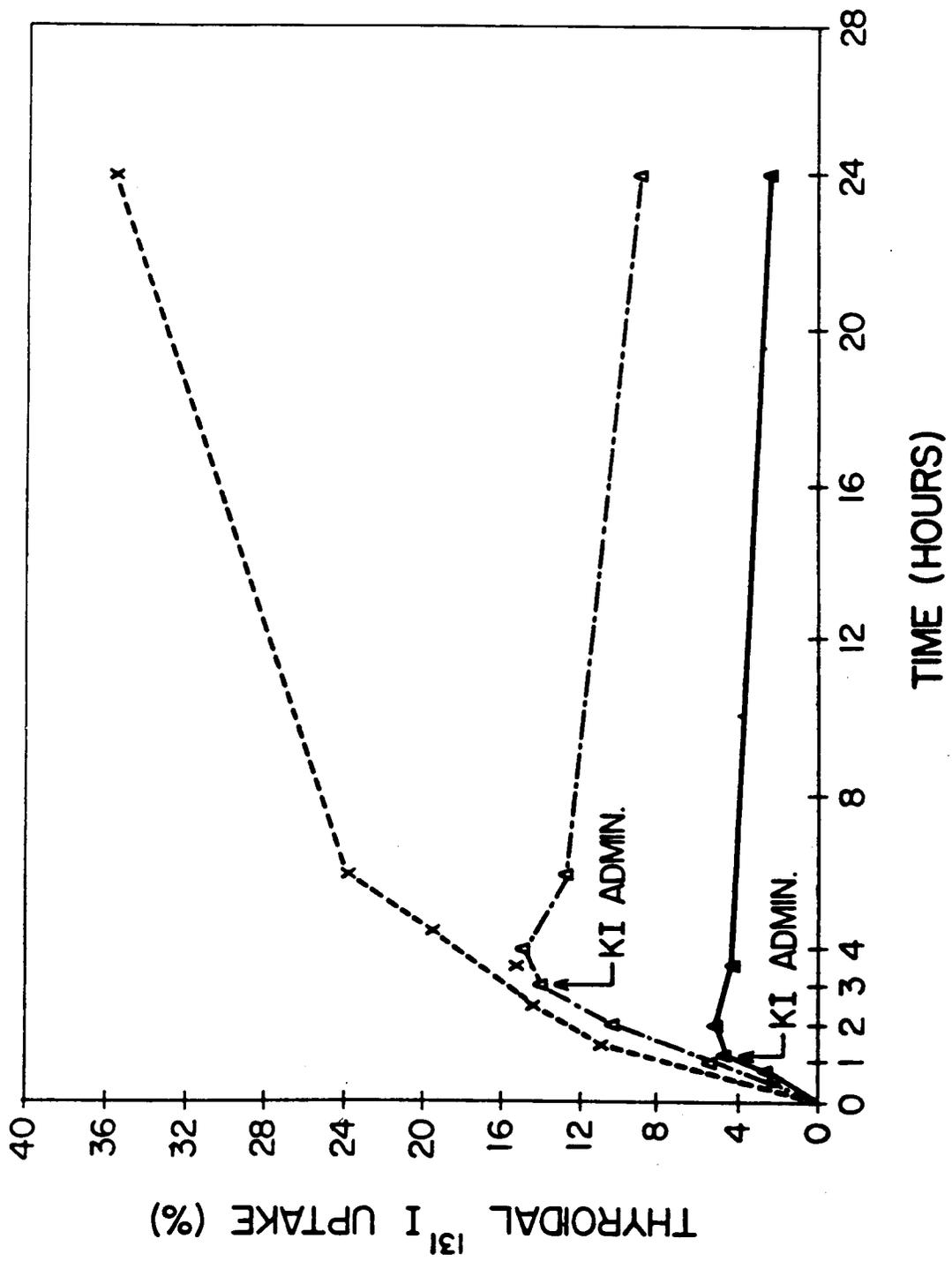


FIGURE 3

EFFECTIVENESS OF SINGLE DOSE KI ADMINISTERED BEFORE ^{131}I IN LOWERING THYROIDAL UPTAKE

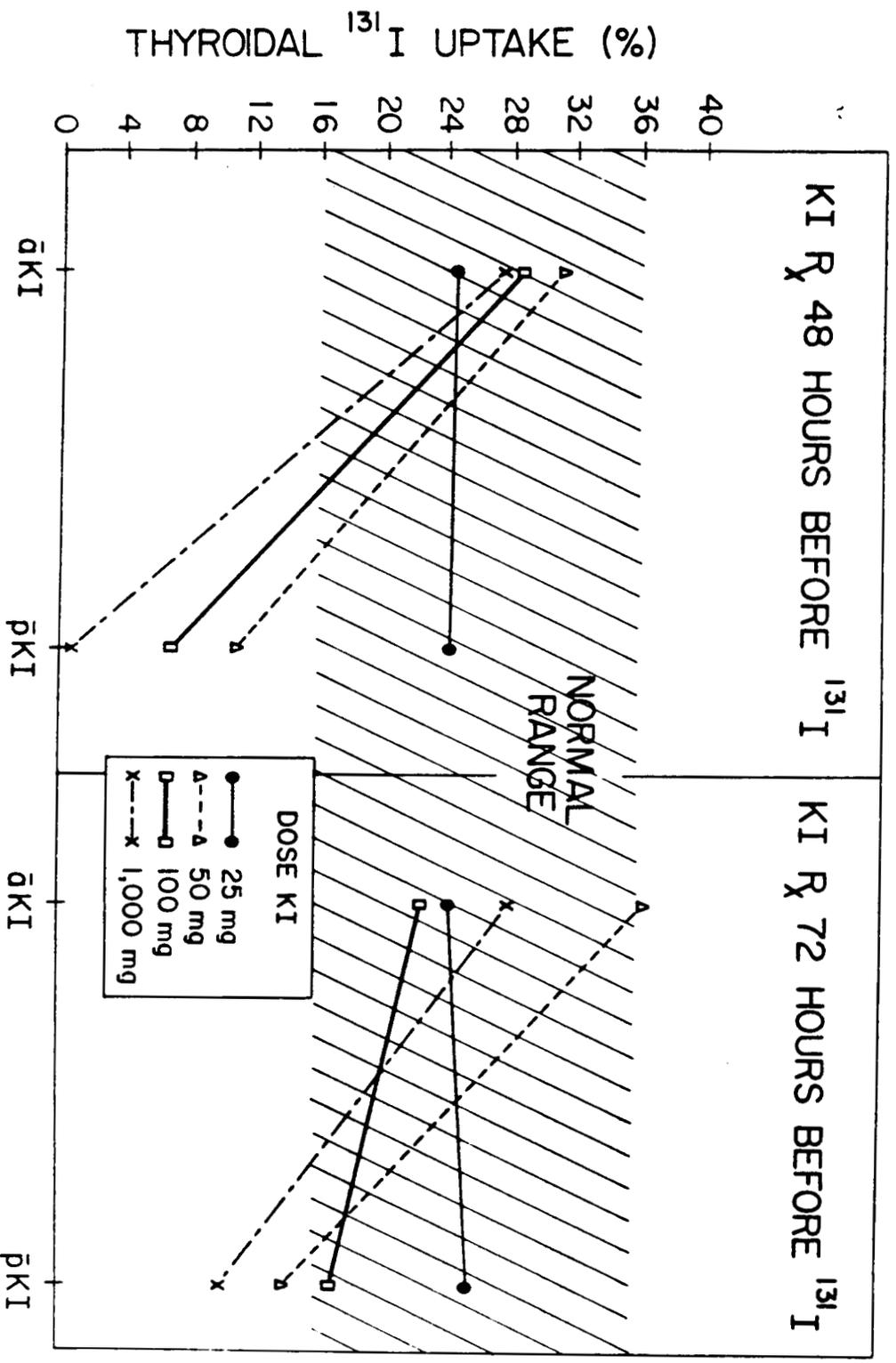


FIGURE 4

RELATIONSHIP BETWEEN % SUPPRESSION AND SERUM IODIDE CONCENTRATION

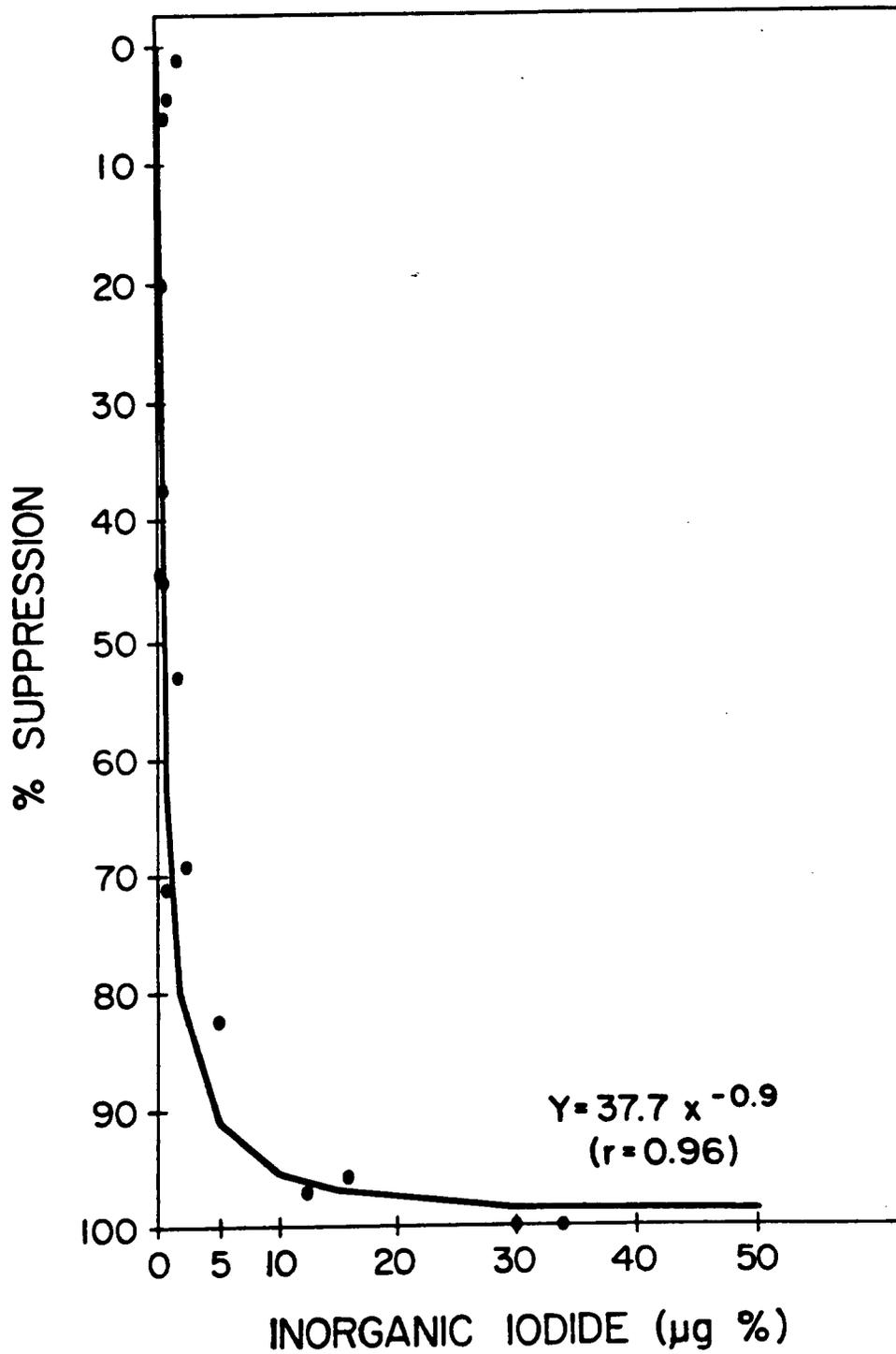


FIGURE 5