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Catabolism and Tissue Distribution of CD^{109} in Rats

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There have been a number of reports in the literature concerning the uptake and distribution of cadmium by different tissues following various routes of exposure (SHAIKH & SMITH 1980; RAHOLA et al. 1972, 1973; MCLELLAN et al. 1978). From a whole body retention study in rats, MOORE et al. (1973) calculated the biological half-life from the second component to be 252 for iv and 175 for ip and 200 days for inhalation exposure, respectively. The first component was considered to be the phase responsible for the rapid elimination of unabsorbed cadmium. BURCH & WALSH (1959) have also shown that most unabsorbed cadmium accumulates in the GI tract at a very early stage, possibly within 4 hours of injection before being excreted. We have reported earlier that following a 4 hr sc cadmium exposure, lung damage can be induced in mice and rats (CHOWDHURY et al. 1982, 1983). The catabolic fate of the cadmium in these early events appeared to be very important as the damage seen in the lung may be either cytotoxic or due to direct tissue deposition of cadmium in lung tissues. Further studies on rats for a 72 hr exposure period also indicated that significantly large amounts of cadmium remain deposited in the organs of gastrointestinal tract, lung, liver and kidney (CHOWDHURY et al., submitted for publication). Our present study is concerned with the catabolic fate of cadmium at early time periods via a bolus or constant infusion and its simultaneous organ distribution in the same experimental animal.

MATERIALS AND METHODS

Twelve rats of approximately 200-225 g of body weight in each group (bolus or constant infusion groups) were used in this study. The rats were deprived of food 24 hrs prior to the study. For bolus exposure, each animal was anesthetized with Nembutal (30 mg/kg) and secured in the rat board. The jugular vein was then exposed and a catheter was placed to inject a solution of cadmium-^{109} containing 3.75 μc/μg Cd. The abdomen was then exposed and abdominal aorta was cannulated to collect blood samples. The blood samples were withdrawn at 0, 2, 4, 6, 8 and 10 min following the injection. Subsequent blood collections were made at every 5 min intervals until 120 min. The animals were then sacrificed with an overdose of Nembutal and tissue samples of lung, liver, kidney (both right and left), heart, brain, muscle and organs of the gastrointestinal tract (fundus, antrum duodenum, jejunum, cecum, colon and pancreas) and esophagus were promptly collected, weighed and processed for radioactivity.

For constant infusion experiments, the animals were injected for 50 min with a solution of Cd^{109} (3.75 μc/μg Cd) with constant pump flow rate of 7.52 ml/hr. Samples at every 5 min were collected and radioactivity measured immediately to determine a steady state distribution of counts in 0.5 ml blood samples. The infusion was stopped after it was noted that blood cadmium level reached a steady state. Collection of blood samples following the withdrawal of pump at steady state were continued at 10 min intervals until 120 min. The animals were then sacrificed with an overdose of Nembutal and all tissue samples, as described in earlier sections, were carefully and promptly collected and processed for radioactivity measurements.

Counts obtained for both blood and tissue samples were corrected for normal controls and percent distribution of Cd^{109} was calculated from the total counts injected into the total counts found for each organ. The percent of Cd^{109} distribution was then normalized for per gm of organ weight.

The Student's "t" test was used to determine the significant differences (SNEDECOR & COCHRAN 1967). A p value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

The catabolism of Cd^{109} in blood injected either as a bolus or as a constant infusion is shown in Figure 1. Following a bolus injection (left diagram), the Cd levels in blood rose immediately and fell rapidly between 0-10 min. Cd levels showed a gradual decline until 90 min of collection and produced a total of three experimental slopes. The T ½ values calculated from slopes I, II and III are 3.4, 17.5 and 51.7 min, respectively. Linear regression analysis on the entire curve produced a mean slope of -0.009, r = -0.65 and a mean T ½ = 77 min. The catabolic fate of Cd^{109} following a steady state distribution of Cd^{109} by constant infusion, has been shown in the right column. Two distinct slopes can be assessed from the Cd-disappearance curve. The T ½ values calculated from these two slopes are 6.3 and 37.9 min, respectively. Linear regression analysis on the entire curve produced a slope of -0.005, r = -0.87 and a mean T ½ = 131.3 min.

Simultaneous uptake of cadmium^{109} in various organ compartments following either bolus or constant infusion is shown in Figures 2-5. Figure 2 shows percent Cd^{109} distribution in muscle, brain and heart. Relatively little amounts of cadmium were accumulated in muscle and brain. The accumulation in the heart is in the range of 0.2-0.24%. Compared to distribution in muscle, via both methods of administration, brain and heart, showed no significant differences. Figure 3 shows the distribution of Cd^{109} in target organs of liver, kidney and lung. Cd^{109} distribution in lungs via both methods of exposure was found to be 0.1-0.2%. The distribution found in liver and kidney was very high and is in the range of 4-5% for liver and 0.5-0.9% for kidney. Comparison of the distribution pattern of liver, lung and kidney via either routes of administration did not reveal significant differences.

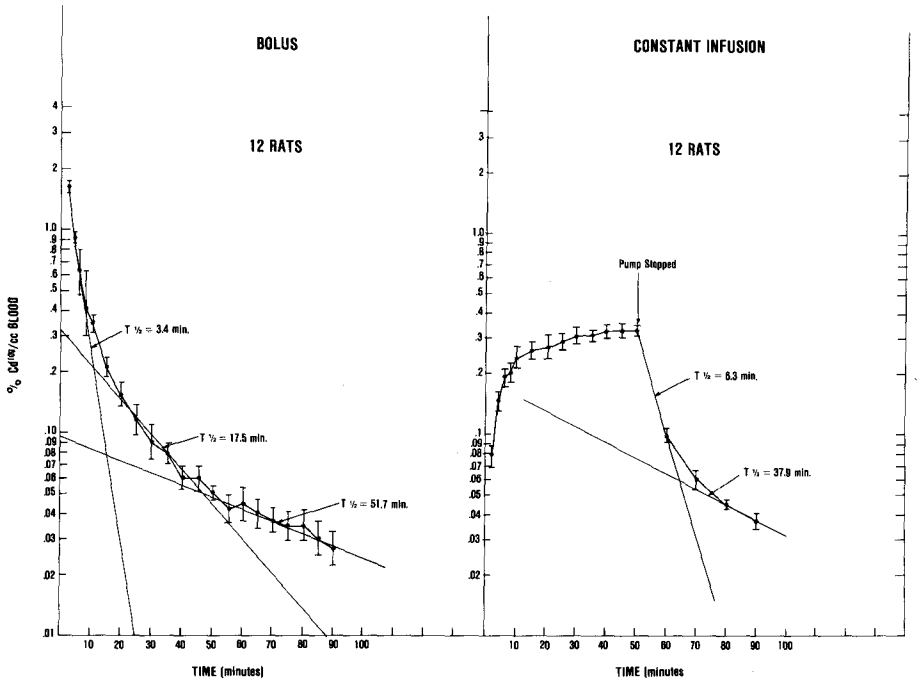

Figure 1. Distribution of Cd^{109} in blood. Bolus injection (left diagram) and constant infusion (right diagram).

Figure 4 shows the distribution pattern of Cd^{109} in esophagus, fundus, antrum and pancreas. Less than 0.1% of cadmium was distributed in the esophagus and antrum. The distribution of Cd in the fundus was 0.3%, and in pancreas 0.36-0.59%. Statistical evaluation of esophagus, fundus, antrum and pancreas via either method of administration revealed no significant differences.

Studies on the distribution of Cd^{109} in small intestine are presented in Figure 5. The greatest amount of Cd was retained in the duodenum (0.77-1.0%) with lesser concentration in the jejunum (0.61-0.67%) followed by colon (0.29-0.34%) and cecum (0.2-0.28%). Total accumulation of Cd^{109} by the organs of the GI tract including pancreas was greater than any other organs except for the liver.

Cadmium retention by various organs that occurs due to industrial and environmental air pollution presents a potential health problem as Cd is known to induce a variety of pathological conditions (CHANG et al. 1981; HIETANAN 1981; FRIBERG et al. 1971, 1973). Our animal data, as observed in blood and tissue of rats following an acute exposure indicate that besides lung, liver and kidney, Cd is accumulated to a large extent in the GI tract. These data are consistent with the accumulation observed by other investigators in those organs (MOORE et al. 1973; DECKER et al. 1957; FRIBERG et al. 1971, 1973). Cadmium retention data obtained by previous investigators are based mainly on the long-term chronic studies (SHAIKH & SMITH 1980; RAHOLA et al. 1972, 1973; FRIBERG et al. 1971, 1973).

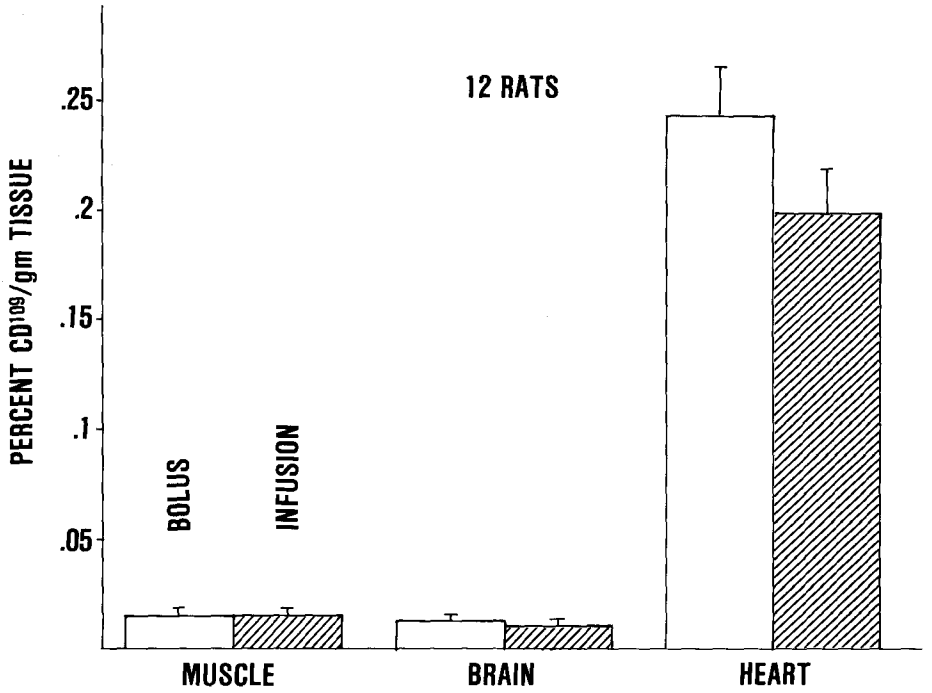

Figure 2. Distribution of Cd (percent Cd^{109}/gm tissue) in muscle, brain and heart. ☐ - Bolus injection; ▨ - Constant infusion.

Reports from these studies estimate the half-life of Cd by various routes of administration from days to years (SHAIKH & SMITH 1980; FRIBERG et al. 1971, 1973; MCLELLAN 1978). However, studies reported on short-term Cd induced lung damage from our laboratory convinced us to delineate further the importance of half-time estimation during early exposure periods. Results from our present study indicate three phases of Cd catabolism. The rapid phase of our bolus study (Figure 1) may represent the excretion of unabsorbed Cd by the GI tract. The slower phase more accurately represents absorption and retention. The longer half-time as observed in steady state distribution studies may possibly indicate the cellular saturation and redistribution of Cd in tissues. GARTY et al. (1981) recently demonstrated a redistribution of Cd in blood of rats following an intravenous injection. No significant difference in uptake of Cd in blood can be accounted for via either methods of administration suggesting that the distribution of Cd is very rapid and rather independent of organ blood flow. Although lung showed a retention of 0.1-0.2%, this amount of deposition in pharmacological dose dependent situations would be sufficient to induce a demonstrable pathologic damage as shown elsewhere (CHOWDHURY et al. 1982, 1983). The

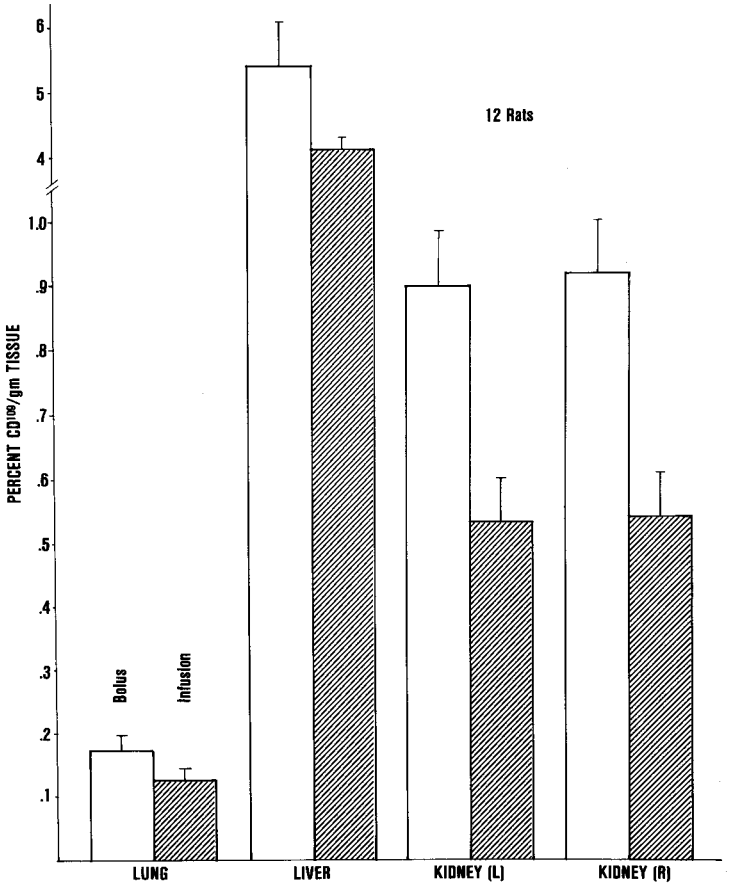

Figure 3. Distribution of Cd^{109}/gm of lung, liver, kidney (L) and kidney (R). ☐ - Bolus; ▨ - Constant infusion.

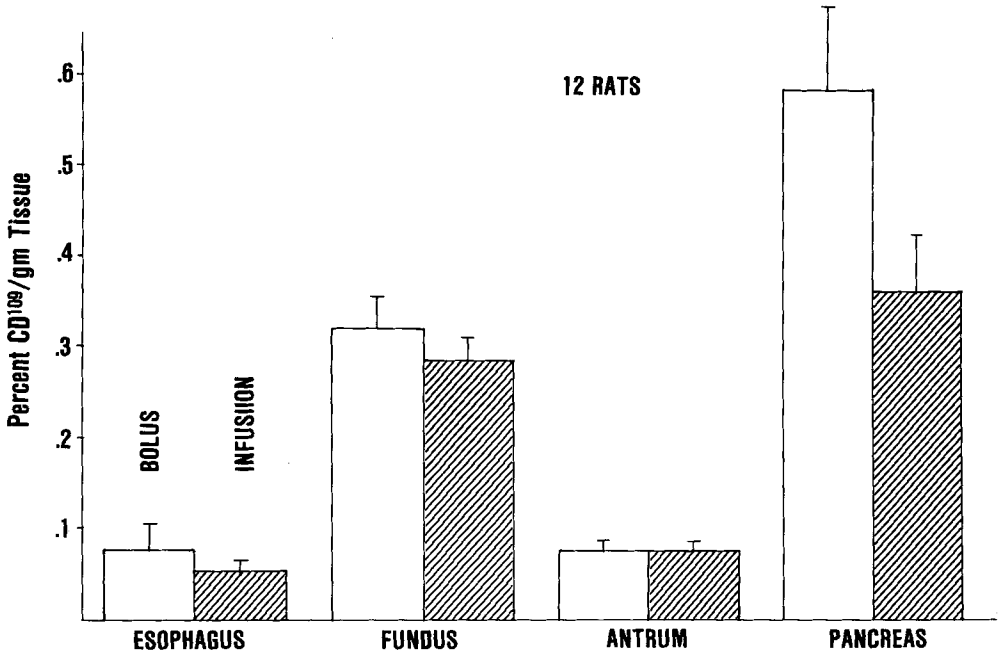

Figure 4. Distribution of Cd^{109}/gm esophagus, fundus (stomach), antrum (stomach) and pancreas. ☐ - Bolus; ▨ - Constant infusion.

mechanism of retention of cadmium by certain parts of the GI tract are not yet clear. However, identification of intestinal and pancreatic metallothionein suggests the biosynthesis of Cd-binding proteins by these organs (NOMIYAMA & NOMIYAMA 1982; YAU & MINNEAR 1977). Not much information is available on the esophageal, fundus and antral Cd-binding proteins; however, ONOSAKA & CHERIAN (1981) recently reported significant increases in the metallothionein concentration in stomach of rats exposed to three doses of $CdCl_2$ suggesting the cadmium-binding protein synthesis by these organs.

Retention of Cd by liver and kidney has been extensively investigated (KAGI & NORDBERG 1979; WEBB 1979; SYVERSON 1975). The accumulation by liver or kidney is known to be due to the presence or production of Cd-binding protein, metallothionein. Further studies demonstrated that the time period required for induction of Cd-binding protein following exposure are in the range of 6-8 hours (FRAZIER & PUGLESE 1978). Since the data obtained in this investigation are based on a 2 hr study, it would be difficult to reconcile the involvement of metallothionein as a major factor to retain Cd^{109} by GI tract organs. Cd-uptake by the GI tract or stomach counterparts may, therefore, be associated with mucosal cells for which more direct evidence will be necessary. We have shown in our earlier studies in dogs that intravenous Cd-administration may result in the release or suppression of GI hormones (CHOWDHURY et al. 1981). It

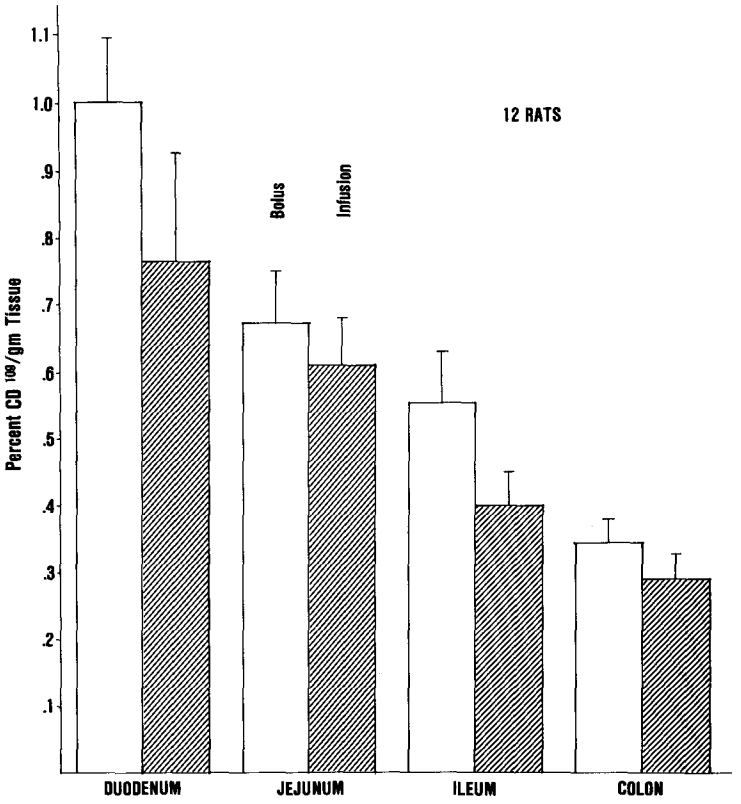

Figure 5. Distribution of Cd^{109}/gm of duodenum, jejunum, ileum and colon. ▭ - Bolus; ▨ - Constant infusion.

may be possible that Cd-uptake by the cells of duodenum, jejunum, ileum, colon or pancreas may be responsible for either the release or inhibition of these gastrointestinal hormones in the GI tract.

Greater accumulations of cadmium observed at such early periods may explain some phenomenon or pathogenesis in renal hepatic and pulmonary lesions observed with industrial workers acutely exposed to cadmium.

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