THE EFFECTS OF OVER-THE-COUNTER DRUGS ON CHROMIUM ABSORPTION IN RATS

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CHAPTER I

INTRODUCTION

Chromium is an essential trace element for animals and humans. Evaluation of chromium status in humans is difficult because circulating chromium may not be in equilibrium with tissue stores. Chromium measurement requires careful sample handling and sophisticated instrumentation (1). Due to these limitations, relatively few data are available on chromium intake, absorption and excretion in humans. Data on drug-chromium interactions are not available.

Significance of the Problem

Chromium intake varies widely. Estimated chromium intake ranged from 24.5 μg/day in England (2), 29 μg/day in Finland (3), 56 μg/day in Canada (4), to 240 μg/day in Belgium (5). In more recent international studies intakes below 100 μg/day were reported (6). In the United States estimated mean chromium intake ranged from 25-89 μg/day (7, 8) compared to the safe and adequate daily dietary intake of 50-200 μg per day (9).

Processing and refining usually reduced chromium in foods (10, 11) with estimates of chromium losses of up to 80

percent for some foods (11). Consumption of highly processed foods may result in marginal chromium intake and depletion of chromium stores. The elderly are at particular nutritional risk because of their reduced energy needs and decreasing absorptive capacities. Studies of chromium supplementation in elderly subjects (12, 13) suggested that U.S. dietary intakes may be inadequate to maintain tissue chromium levels throughout life.

Insufficient chromium intake may be responsible for some of the glucose intolerance associated with aging (14, 15). The long-term suboptimal chromium intake may cause the decrease in tissue chromium with age and contribute to the incidence of non-insulin dependent diabetes and atherosclerosis observed in the United States (16).

The elderly may be particularly at risk for adverse drug-nutrient interactions because of their chronic use of medications. Gastrointestinal disorders may promote antacid abuse in the elderly. Many post-menopausal women take calcium-based antacids such as Tums to increase their calcium intake. Antacid preparations are commonly prescribed in order to reduce gastrointestinal blood loss associated with aspirin therapy in the treatment of arthritis. Additionally, many commercially available aspirin formulations contain antacids (i.e.; Bufferin). Advertising further encourages over-the-counter drug abuse. These trends may exacerbate existing problems associated with marginal dietary intake of chromium in humans.

This study was designed to evaluate the effects of distilled water (control), Tums, Maalox, vitamin C, aspirin and Bufferin on absorption, retention and excretion of ^{51}chromium from $^{51}CrCl_3$ in female rats.

Objective

The following research objective was developed for the proposed study:

1. to determine if selected over-the-counter drugs (Tums, Maalox, vitamin C, aspirin and Bufferin) alter absorption, retention or urinary excretion of ^{51}Cr from $^{51}CrCl_3$ in female rats.

Hypothesis

The following hypothesis was developed for this study:

1. There will be no statistically significant differences in absorption, retention or urinary excretion of ^{51}chromium from $^{51}CrCl_3$ due to a dose of distilled water, Tums, Maalox, vitamin C, aspirin, or Bufferin.

Limitations

This study involved a single therapeutic dose of Tums, Maalox, vitamin C, aspirin and Bufferin. Thus, the long term effects of these drugs were not explored. The pharmacodynamics of many drugs are dose-dependent. Dosage form characteristics as well as a range of concentrations

were not investigated. Thus, the data we obtained, while significant, are not generalizable due to the single dose. Another limitation is the use of an animal model rather than human subjects.

CHAPTER II

REVIEW OF LITERATURE

Over-the-Counter Drug Interactions in the Elderly

A Brief History of Aspirin

Man's practice of self-medication is deeply embedded in history. Around 400 B.C. Hippocrates suggested that women should drink an extract from the leaves of the willow tree to lessen the pain of childbirth (17). In the 19th century the active agent from the willow tree was identified as salicylic acid. In 1860 salicylic acid was synthetically manufactured but unpatentable due to its extreme gastrointestinal irritation with continuous use. In 1900 the derivative acetylsalicylic acid which is less irritating was synthesized and patented by Farbenfabriken Bayer, founder of the Bayer company (18). Since the early 20th century aspirin has been used in clinical medicine in reducing pain, fever, and inflammation.

Clinical Uses of Aspirin

In recent years, results of some studies have suggested that aspirin might prevent heart attacks and strokes (19-26), slow the formation of cataracts (27-33), and perhaps

even diminish the incidence of pregnancy-induced hypertension and pre-eclampsia (34-36). At the same time, many clinicians have urged that children with flu or chicken pox not be given aspirin because such children may face an increased risk of Reye's syndrome, which can be fatal (37-38). More recently, salicylates have been implicated in Reye's syndrome in adults (40-41). Data linking aspirin to gastrointestinal ulceration and gastrointestinal bleeding have emerged as well (42-44).

Aspirin is most frequently taken to lessen pain, lower fever, or reduce inflammation of arthritis and rheumatic fever. Rheumatoid arthritis, found among all age groups, affects at least 6.5 million Americans. Women are affected about three times as frequently as men (17, 39, 45). Although rheumatoid arthritis is more severe, it is not as common as osteoarthritis. The latter is more degenerative than inflammatory and mainly affects the body's weight-bearing joints (spine, hips and knees). At least 16 million Americans need medical care for osteoarthritis. Over age 45, osteoarthritis prevalence is greater in women than men (17, 39, 45, 46).

Despite the introduction of newer non-steroidal anti-inflammatory drugs, aspirin remains the drug of choice or at least the initial drug for treatment of both arthritic conditions (17, 45). According to the July, 1982, Consumer Reports, arthritis sufferers "consume about half of all aspirin sold". However, because high doses of aspirin are

required in the treatment of arthritis, the side effects of the drug, especially irritation of the stomach, can become a major problem for some patients.

The Gastric Barrier and Aspirin

Absorption from the stomach is normally very limited. This low level of absorption is mainly attributed to highly resistant mucosal cells that secrete a viscid and adherent mucus and the very tight junctions between the adjacent epithelial cells that line the gastric mucosa (47). Competent tight junctions prevent diffusion of contents of the gastric lumen between the mucosal cells into the interstitial fluid.

The gastric mucosal barrier has physiochemical properties similar to those of all other cells; it is a lipid and protein layer penetrated by very few water-filled channels. In contrast with water-soluble molecules, which are restricted to water filled channels, fat-soluble compounds can cross a lipid-containing membrane by dissolving in the lipid. Consequently, some compounds are water soluble at one pH and fat-soluble at another. Aspirin (acetylsalicylic acid) is an example. Aspirin has a pK_a of 3.5. When the drug is dissolved in a solution whose pH is higher than 3.5, more than half the carboxyl groups are ionized, and at pH 6 virtually all the salicylate molecules are negatively charged. In this state (negatively charged at pH 6), the molecules are water soluble, and their passage

across the mucosa is restricted to water-filled channels. When aspirin is dissolved in a solution with a pH below 3.5 it is un-ionized and fat soluble; it then dissolves in the lipid-protein layer and is rapidly absorbed from acid gastric contents (48).

Aspirin damages the gastric mucosal barrier as it is absorbed. Davenport (49) hypothesized that the aspirin disrupts the lipid-protein layer on the surface of the cells, and it causes desquamation by breaking the tight junctions between cells. As a consequence, the mucosa becomes abnormally permeable to water-soluble compounds and ions. Hydrogen ions move rapidly through the damaged barrier, and their flow is facilitated by exchange for sodium. Entry of hydrogen ions into the mucosa exacerbates damage caused by the aspirin and destruction of the mucosa follows. Potassium and organic cell contents enter the lumen, followed by sodium and chloride from the interstitial fluid. Upon further destruction of barriers, a fluid containing glucose and plasma proteins flows from the interstitial spaces and capillaries. When the mucosa is damaged it also releases histamine. Histamine is a vasodilator, and it increases capillary permeability. Both effects promote capillary filtration; consequently interstitial volume and pressure rise, and fluid is forced through the relatively larger channels opened by mucosal injury. Aspirin opens the gates of the mucosal barrier, and acid pouring through the breached defenses destroys

capillaries and venules. Finally, after the most severe damage, bleeding occurs.

Aspirin and Antacid Interactions

In an attempt to ameliorate deleterious effects on the gastroduodenal mucosa, numerous modifications in aspirin administration have been studied. These have included administration of aspirin in an enteric-coated form, buffered, or simultaneous administration of antacids, cimetidine or prostaglandins to reduce the gastric absorption and irritation of aspirin (50-52).

Addition of an antacid to aspirin therapy results in a "buffer zone" of increased pH immediately around the dissolving aspirin particles. This buffer-zone enhances the dissolution of the aspirin particles and decreases the local irritation by the undissolved aspirin particles. More rapid absorption and higher peak levels in the blood were achieved with the administration of commercially available effervescent tablets, the soluble salt of aspirin, sodium acetylsalicylate, and preparations containing aluminum and magnesium buffers than with standard preparations of aspirin (53). Also aspirin from an enteric coated preparation was absorbed more rapidly when given concomitantly with an aluminum hydroxide-magnesium hydroxide combination antacid (50).

Gaspari et al. (54) found that both aluminum hydroxide-magnesium hydroxide and calcium carbonate containing

antacids modify oral aspirin pharmacokinetics in uremic patients on hemodialysis. The lower plasma aspirin concentrations associated with antacids in uremic patients, however, were the consequence of a slow absorption rate, rather than of rapid hydrolysis in the circulation. The potential chemical interactions between aluminum ions released by the antacids and the aspirin molecule may explain the results obtained with the aluminum-containing antacids. Aspirin reportedly formed a water- insoluble complex with aluminum making the limiting step for absorption the rate of release of free acid from the complex. Levy and Sahli (55) confirmed that the aluminum salt of acetylsalicylic acid was absorbed more slowly than the acid form of the drug.

Hogben et al. (56) demonstrated in detail that drugs that are weak electrolytes may be quickly absorbed from acid gastric contents if they are un-ionized and fat soluble in acid solution. For example, at pH 2, acetylsalicylic acid (pK_a 3.5) is more than 95 percent in the un-ionized, fat soluble form, and it diffuses readily across the mucosa. At pH 7 acetylsalicylic acid is completely ionized and fat insoluble; it is poorly absorbed from the stomach. This could explain the interference between the aspirin and calcium carbonate since aspirin absorption is partially pH dependent. However, other data indicated that buffered solutions of aspirin were as completely and rapidly absorbed as unbuffered solutions (57-58). More rapid emptying of the

buffered solutions into the duodenum and the resultant larger absorptive area supposedly compensated for the reduced gastric absorption.

Cytoprotection by Prostaglandins

Prostaglandins also may be useful for preventing or reducing aspirin-induced mucosal damage. Prostaglandins are distributed widely throughout the gastrointestinal tract and influence a number of gastric and intestinal functions. Robert and coworkers (59) reported that certain prostaglandins prevented experimental damage to gastric mucosa by a variety of noxious agents, including aspirin.

In initial clinical studies, oral administration of 1.0 mg of prostaglandin E_2 (PGE_2) four times daily before aspirin ingestion prevented increased fecal blood losses in healthy volunteers (60). In another study, aspirin-induced upper gastrointestinal blood loss, measured by serial gastric washing, was decreased ($p<0.05$) during the second day after administration of PGE_2 (51). Gilbert and colleagues (61) indicated that prostaglandin pretreatment prevented endoscopically visible severe gastric mucosal injury after single-dose aspirin administration.

The physiologic mechanisms by which prostaglandins protect the gastric mucosa from damage by non-steroidal anti-inflammatory drugs are not known. The chief cytoprotective role of prostaglandins may be to increase the secretion of mucus (62). Other hypotheses have included

activation of gastric mucosal adenyl cyclase, alteration of gastric mucosal blood flow or tightening of the gastric mucosal barrier; however, these hypotheses for protective effects remain speculative (63-66).

Antacids

Antacids are commonly prescribed by clinicians for treatment of peptic ulcers, reflux esophagitis and hyperchlorhydria. Antacids enhanced healing of ulcers to the same degree as other active drugs. Initially, the efficacy of antacids was demonstrated at high doses. Recent studies have indicated that doses with low neutralizing capacity promote ulcer healing (67, 68). This raises the question of whether the mechanism of action actually involves neutralization of the luminal acid.

Cytoprotection by Antacids

Aluminum hydroxide may be cytoprotective. Szelenyi et al. (69) and Tarnawski et al. (70) reported an increased concentration of prostaglandin E_2 (PGE_2) in the gastric contents of rats after intragastric administration of high doses of antacids containing aluminum hydroxide and magnesium hydroxide. An elevated PGE_2 concentration in the gastric juice may indicate increased gastric synthesis of PGE_2 and enhanced cytoprotective activity (71, 72).

Confirming previous observations by Szelenyi et al. (69) and Tarnawski et al. (70), Berstad et al. (73) noted

increased intraluminal concentration of PGE_2 in response to intragastric administration of both high and low doses of aluminum-hydroxide-containing antacids. Low doses of antacids, comparable to therapeutic low dose regimens in man, also increased the concentration of PGE_2 in the gastric content.

If increased intraluminal PGE_2 concentration reflects increased mucosal synthesis of PGE_2, antacids not only may neutralize gastric acid but also may stimulate mucosal PGE_2 synthesis. A high dose of aluminum hydroxide released more PGE_2 when given alone than when given in an antacid mixture with magnesium hydroxide and calcium carbonate. These results support the concept proposed by Szelenyi et al. that PGE_2 release was a specific effect of aluminum hydroxide and not a general effect of antacids (69).

Self-prescription of Antacids

The majority of antacids consumed are obtained over-the-counter (OTC) or "self-prescribed" for treatment of either the occasional "upset" stomach or a variety of other symptoms (74). However, "heartburn" and "indigestion" may indicate ischemic heart disease rather than a gastrointestinal disorder. Temporary relief from OTC medications often gives the patient a false sense of security and delays appropriate medical intervention (75).

Excessive use of aspirin, antacids and other over-the-counter drugs without medical supervision may be dangerous.

Abuse of OTC drugs may be most detrimental to the elderly because they consume a disproportionately high percentage of all drugs. In 1982, only 8% of the population was 70 years or older, yet this age group used 22% of all drugs (76). These data may underestimate drug consumption because reports used by the Food and Drug Administration (FDA) did not include all outlets for over-the-counter drugs. Data were limited to the hospital and drug store markets which may represent only 40% of total sales for a drug such as aspirin (76).

In 1986, approximately 11.7% of the population were 65 or older; yet, 31% of all drugs were prescribed for this age group. Seventy-five percent of the population over 65 also reported using non-prescription or over-the-counter drugs (77). These data represent an increase in the population 65 and older as well as an increase in their chronic drug consumption.

Frequently, the elderly patient does not inform or consult the physician regarding concomitant self-medication with OTC products (78). Guttman (79) found that only 12% of the elderly patients using OTC drugs had consulted a physician about their use. Also clinicians frequently fail to document reported OTC usage by the elderly patient (80).

Chaiton and colleagues (81) found that nearly 60% of an elderly study population used OTC drugs, with women using them more often than men. Guttman (79) found that two-thirds of elderly ambulatory patients used OTC drugs. More

than 50% of these drugs were oral analgesics. In another sample of 244 people more than 60 years of age, analgesics were most commonly used (66.6%), followed by cardiovascular agents (33.5%), laxatives (30.6%), vitamins (29.3%), antacids (26.4%) and anti-anxiety agents (22.3%) (82). Forty percent of the total medications taken were OTC drugs. Eighty-three percent of these clients were also taking two or more drugs. The most common drugs used by women were sedative-tranquilizers, followed by hormones and gastrointestinal agents. The most frequent categories in men were analgesics, sedative-tranquilizers and cardiovascular drugs.

Because OTC drugs are easily purchased, most people regard them as harmless. However, the simultaneous use of OTC drugs with other prescribed drugs may result in side effects or toxicity (77, 78, 83-85). "Of more than 4,000 drug abuse studies of elderly patients between 1926 and 1975, 10% dealt with adverse pathologic and physiologic effects from inappropriate OTC usage" (75). Aspirin was cited most often, but antacids and other OTC drugs were implicated as well.

Aspirin-Drug Interactions

Adverse effects from aspirin are not common but the frequency with which aspirin is taken, alone or in multiple-drug compounds explained its repeated involvement (86-88). Aspirin inhibits the uricosuric effects of probenecid and

sulfinpyrazone, may enhance the hypoglycemic effects of sulfonylureas, decreases both clearance and plasma protein binding of methotrexate thereby increasing the drug's toxicity, and may cause an increased risk of hemorrhage when taken with prescription anticoagulants such as warfarin (75, 89).

Antacid-Drug Interactions

Antacids may result in slow or incomplete absorption, may have no effect on drug absorption, or may increase the rate or amount of drug absorbed resulting in toxicity. The most clinically significant adverse effect of antacids is the decreased absorption of drugs such as iron, tetracyclines, cimetidine (Tagament), and digoxin (Lanoxin) (90). In addition, antacids may increase the pH of the urine and therefore influence the elimination kinetics of other drugs (91). Because of the variability among individuals, predicting the effect of an antacid on absorption of a particular drug can be difficult.

Drug-Induced Hospitalizations

The Royal College of Physicians estimated that adverse drug reactions were responsible for 20 to 25 percent of all elderly patient admissions to acute- care hospitals in England (92). In the United States, adverse reactions in the elderly account for between 12 and 17 percent of hospital admissions (78).

Canadian data indicated that 30 percent of all elderly patients admitted to acute-care facilities from nursing homes suffered from adverse reactions to drugs, while British studies suggested that 40 percent of elderly persons living in the community were affected by adverse drug reactions (77). The use by the elderly of a greater number of drugs increases the probability of adverse reactions. The frequency with which OTC drugs were responsible for illnesses leading to hospitalization emphasizes the fact that OTC medicines, alone or in combination with prescription drugs can produce severe reactions.

Advertising and Over-The-Counter Drugs

Over-the-counter (OTC) drugs used knowledgeably can contribute to the well-being of the elderly. Unfortunately, statements made in advertising are not necessarily accurate. Even quotations taken from published reports and clinical studies can be taken out of context thereby misleading the consumer. Possible beneficial effects of a drug or product are often publicized long before they are confirmed. Examples of this include oat bran to lower cholesterol, Metamucil to increase dietary fiber, Tums as a calcium supplement and aspirin in the prevention of heart attacks. Thus, the elderly should seek knowledgeable and unbiased advice about drug regimens.

Drug-Nutrient Interactions

Data indicate that health, social and economic problems of the elderly, especially those over age 75, are predominantly the problems of women. Furthermore, old age is associated with women living alone on reduced incomes and in increased poverty, accompanied with a greater risk of ill health, institutionalization, and death (89).

Elderly women consume a greater percentage of all drugs than men. Many elderly people, primarily women with osteoporosis or those fearing osteoporosis, take calcium supplements either as calcium lactate, calcium carbonate or calcium gluconate. Many calcium supplements release calcium ions that are absorbed and can cause clinically important hypercalcemia, rebound acid hypersecretion, constipation, and a variety of other interactions.

Adverse metabolic and nutritional effects of antacid abuse in the elderly are eloquently and extensively reviewed by Roe (83-85). Briefly, hypophosphatemia has been reported with excessive use of aluminum and magnesium hydroxide containing antacids, while aluminum containing antacids are associated with increased intestinal and urinary excretion of calcium. Additionally, magnesium intoxication was reported in patients with chronic renal failure who took magnesium containing antacids.

Conventional doses of antacids normally cause few adverse reactions. However, frequent and prolonged use with larger doses becomes more significant.

Drug-Mineral Interactions

Freeman and Ivy (94) reported that calcium carbonate and aluminum hydroxide reduced the retention of iron fed to anemic rats, while other researchers have reported decreased absorption of iron after administration of antacids to normal subjects (95). Uncoated aspirin caused iron-deficiency anemia in the elderly by inducing blood loss from the gastrointestinal tract (83, 89).

Commonly used OTC drugs (as well as prescription drugs) can affect mineral status and have the most impact on minerals that are marginal in the diets of the elderly. Impaired absorption of nutrients in the elderly has been reported (96). Chromium is an essential trace element for animals and humans. Insufficient dietary chromium leads to signs and symptoms similar to those associated with diabetes and/or cardiovascular diseases (97).

The dietary chromium intake of normal individuals is often less than the suggested minimum intake. Recent studies (7, 8, 98, 99) have estimated mean chromium intake in the United States to be 25-89 ug/day compared to the estimated safe and adequate daily dietary intake of 50-200 ug per day (9). Dietary chromium is not readily absorbed (98, 100-101).

Unfortunately, data on drug-chromium interactions are not available. Because chromium is essential, is not readily absorbed, and tends to be low in the average American diet, the effects of commonly used drugs (both prescription and OTC) on chromium absorption need to be investigated.

In this study, adult female rats were used to determine the effects of several commonly used over-the-counter drugs on ^{51}chromium absorption, retention and excretion from $^{51}CrCl_3$. Because circulating chromium may not be in equilibrium with tissue stores, its measurement in humans is difficult. Also, the low concentrations in biological samples require careful sample handling and sophisticated instrumentation for accurate measurement (1). Thus, the use of a radioactive isotope of chromium in an animal model allows more sensitive evaluation of drug-chromium interactions.

CHAPTER III

EFFECTS OF OVER-THE-COUNTER DRUGS ON CHROMIUM ABSORPTION IN RATS

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ABSTRACT

Effects of five over-the-counter drugs on absorption and retention of ^{51}chromium from ^{51}chromium chloride ($^{51}CrCl_3$) were evaluated using adult female rats. In addition to the control group given distilled water (pH 7.89), groups were given vitamin C (5 mg, pH 2.76), Tums (40 mg, pH 9.72), Maalox (40 mg, pH 8.39), aspirin (40 mg, pH 2.74) or Bufferin (40 mg, pH 8.73).

After a 12 h fast, the drugs were administered by gastric intubation (0.5 ml) followed immediately by an oral dose of $^{51}CrCl_3$ (55 μCi) in 0.14 M HCl (50 μl). Urine and blood samples from the tail were collected at intervals.

Twelve hours after dosing animals were anesthetized and exsanguinated. At 12 h ^{51}Cr in blood, urine and tissues was higher ($p<0.0001$) in the aspirin group than in other groups. The group given Maalox had lower ($p<0.0001$) ^{51}Cr in blood, urine and tissues than the other groups. The Tums group was lower ($p<0.0001$) than all except the Maalox group. Increased ^{51}Cr absorption in the aspirin group and decreased ^{51}Cr absorption in the Maalox group did not appear to be mediated solely by pH. Potential effects on Cr status of long-term use of aspirin or antacids need evaluation because over-the-counter drugs may alter Cr absorption.
INDEXING KEY WORDS: Chromium, vitamin C, aspirin, antacids, rats and absorption.

INTRODUCTION

Chromium is an essential trace element for animals and humans. Evaluation of chromium status in humans is difficult because circulating chromium may not be in equilibrium with tissue stores (1). Due to these limitations, relatively few data are available on chromium intake, absorption and excretion in humans.

Chromium intake varies widely. Chromium intakes below 100 ug/day were reported in recent international studies (2). In the United States estimated mean chromium intake ranged from 25-89 ug/day (3, 4) compared to the safe and adequate daily dietary intake of 50-200 ug per day (5).

Processing and refining reduced chromium in foods with estimates of chromium losses of up to 80 percent for some foods (6). Consumption of highly processed foods may result in marginal chromium intake and depletion of chromium stores. The elderly are at particular nutritional risk because of their reduced energy needs and decreasing absorptive capacities. Insufficient chromium intake may be responsible for some of the glucose intolerance associated with aging (7, 21). Furthermore, long-term suboptimal chromium intake may contribute to the incidence of non-insulin dependent diabetes and atherosclerosis observed in the United States (8).

The elderly may be particularly at risk for adverse drug-nutrient interactions because of their chronic use of medications (9-10). Gastrointestinal disorders may promote antacid abuse in the elderly. Many post-menopausal women take calcium-based antacids such as Tums to increase their calcium intake. Antacid preparations are commonly prescribed in order to reduce gastrointestinal blood loss associated with aspirin therapy in the treatment of arthritis. Additionally, many commercially available aspirin formulations contain antacids (i.e.; Bufferin). Interactions of antacids and minerals have not been thoroughly investigated. However, several studies reported that antacids reduced absorption of iron and zinc (11, 12, 19, 20). Vitamin C enhances iron absorption but its effects on

chromium absorption need further investigation. Data on chromium and drug-interactions are not available.

Aspirin is one of the most widely used drugs. In recent years, results of some studies have suggested that aspirin might prevent heart attacks and strokes (13-18). More recently, the media have focused on aspirin and its use in preventing heart attacks and strokes. Thus, aspirin use by the public and especially by the elderly may increase. Advertising further promotes over-the-counter drug use.

The measurement of chromium in humans is difficult.Thus, use of a radioactive isotope of chromium in an animal model allows the sensitive evaluation needed to determine possible drug-chromium interactions. The present study was designed to determine the effects of distilled water, Tums, Maalox, vitamin C, aspirin or Bufferin on ^{51}chromium absorption, retention and excretion in female rats.

MATERIALS AND METHODS

Forty-six female Sprague Dawley rats (Sasco, Inc., Omaha, NE) with a mean weight of 278$\pm$5 g were randomly assigned to six treatment groups. All animals were acclimatized to the animal care facilities before use. Prior to the experiment, rats were fasted overnight (12 h) but allowed access to water. Animals were intubated with 0.5 ml of distilled water (pH 7.89), or solutions/suspensions of Tums (40 mg, pH 9.72), Maalox (40

mg, pH 8.39), vitamin C (5 mg, pH 2.76), Bayer aspirin (40 mg, 2.74), or Bufferin (40 mg, pH 8.73). Immediately after gastric intubation, animals were fed 50 μl of ^{51}chromium chloride (55 μCi) in (0.14 M) HCl by micropipette. Animals were then placed in individual metabolic cages for urine collection.

Approximately 0.5 ml of blood was collected from the tail at 45 min, 1.5 h, 3 h, and 6 h after intubation of the test substance and ^{51}chromium chloride. At 3, 6 and 12 hrs urine samples were carefully collected to avoid contamination with feces. Twelve hours after gastric intubation, rats were anesthetized with ketamine HCl (30 mg/kg) and xylazine (2.2 mg/kg) and exsanguinated. Blood, urine and tissues were sampled and counted in a gamma counter to assess ^{51}chromium chloride absorption, retention and excretion.

Total ^{51}chromium chloride in blood was estimated assuming blood was 7% of body weight. ^{51}Chromium chloride in each tissue and in blood and urine was expressed as percent of the ^{51}chromium dose. Data were analyzed using the Statistical Analysis System (SAS). Log transformations were performed on blood and urine data and square root transformations on tissue data to correct for non-homogenity of variance. The general linear model (GLM) procedure in SAS was used for analysis of variance of the transformed tissue and urine data. A repeated measures analysis was

performed on the blood data. Differences among means were identified using the least significant difference test.

RESULTS

In blood, animals intubated with aspirin had higher ($p<0.0001$) ^{51}chromium than animals given any other test substance, while the Maalox group had lower ($p<0.0001$) ^{51}chromium than all other test substances (Figure 1). The Tums group was lower ($p<0.0001$) than all except the Maalox group. Groups dosed with water, vitamin C and Bufferin had values between aspirin and the two antacids. Animals dosed with Bufferin had more ($p<0.02$) ^{51}chromium in blood than rats dosed with water and tended ($p<0.08$) to be higher than rats dosed with vitamin C. Animals dosed with vitamin C and water were not different ($p>0.50$).

Total cumulative urinary ^{51}chromium after intubation was higher ($p<0.004$) in the aspirin group than with any other test substance, at all intervals and lower ($p<0.02$) in the Maalox group at 6 and 12 h (Figure 2). Vitamin C and Bufferin groups were not significantly different from each other, but were higher than Tums at all intervals. At 12 h, ^{51}chromium excretion of rats dosed with vitamin C was higher than those dosed with water, Tums or Maalox.

Twelve hours after dosing, ^{51}chromium was significantly higher in liver, kidney and spleen in the aspirin group than any other group (Figure 3). In liver, rats dosed with the Bufferin had more ^{51}chromium than rats dosed with Tums

($p<0.03$) or Maalox ($p<0.003$). In kidney, Bufferin was higher than water ($p<0.02$), Tums ($p<0.004$) and Maalox ($p<0.0001$). In spleen, all groups were significantly higher than Maalox but were not significantly different from each other.

In all other tissues sampled [(brain, heart, bone (Figure 4) and eye, ovaries and fallopian tube (Figure 5)], ^{51}chromium was significantly higher in the aspirin group. In brain, eye and fallopian tubes there were no significant differences between the other groups. In heart and bone (Figure 4) and ovaries (Figure 5), the groups dosed with Maalox tended to be lower than all other groups. The other groups were not significantly different from each other.

DISCUSSION

Chromium precipitates in the form of large, insoluble complexes at the alkaline pH of the intestine. Therefore chromium absorption may depend on the efficiency with which suitable ligands protect against complex formation (22). Vitamin C is known to enhance iron absorption by forming soluble-monomeric complexes that prevent precipitation and polymerization (43). The enhancement of calcium absorption by vitamin C occurs in a similar manner. In this study, the increased absorption of ^{51}Cr in the vitamin C group compared with the antacid groups, may be due to ^{51}Cr binding to vitamin C thereby protecting against precipitation and olation. Thus, the increased absorption could be due to the

formation of soluble complexes rather than merely an effect of low pH.

Antacids influence drug or mineral absorption by alteration of ionization state or solubility factors dependent on pH. Antacids also delay gastric emptying and can chelate or adsorb susceptible products. The solubility product of a mineral depends upon the fact that largely insoluble mineral hydroxides form as pH is increased and are in equilibrium with the metal ion at any given pH. An increase in pH or (OH-), causes a decrease in the free metal ion. For instance, iron, like other minerals from the transition series, does not exist in water as an ion but as a hydrate. As the pH is raised the mineral hydrates tend to lose protons and form less soluble hydroxides (23). Thus, the increased pH caused by both Maalox and Tums may be partially responsible for the decreased absorption of ^{51}Cr. However, absorption and metabolism of chromium are also affected by interactions with other metals, especially zinc and iron (20, 24)

The effects of antacids on mineral absorption depend on their components. Freeman and Ivy (11) reported that the utilization of dietary iron was reduced in anemic rats when antacids containing calcium carbonate or aluminum hydroxide were administered. Hall and Davis (19) found that the addition of magnesium trisilicate to a dose of 5 mg of iron as a solution of ferrous sulfate significantly reduced iron absorption. Ekenved and colleagues (12) also reported a

significant decrease in the absorption of iron from ferrous sulfate tablets when administered simultaneously with an antacid suspension containing a mixture of aluminum hydroxide, magnesium hydroxide and magnesium carbonate. This decreased absorption also was explained by a formation of insoluble iron salts at the higher gastric pH induced by the antacids. However another recent report indicated that pH was not the major factor affecting iron absorption (25). A therapeutic dose of liquid antacid containing aluminum hydroxide and magnesium hydroxide had little or no effect on absorption of iron from ferrous sulfate in mildly iron-deficient adults. When the same iron deficient subjects ingested calcium carbonate or sodium bicarbonate with the iron dose, iron absorption was significantly reduced but not totally inhibited. The effect of the carbonates depended more on the formation of insoluble iron-carbonates than on pH.

In the present study, chromium absorption was lower in the group intubated with the antacid containing aluminum hydroxide and magnesium hydroxide (Maalox) than in the group receiving the calcium carbonate antacid (Tums). While chromium does seem to be partially dependent on pH for absorption, other factors may contribute as well to the effect seen with antacids.

Action of antacids on the gastric mucosa is far more general and complex than simple luminal acid neutralization and binding of pepsin. Szelenyi et al. (26) demonstrated

that aluminum hydroxide or its combination with calcium carbonate reduced both hydrogen back diffusion and sodium influx and prevented a fall in potential diffusion induced by taurocholate. Calcium carbonate alone was ineffective. The observed cytoprotective effect of aluminum hydroxide containing antacids was hypothesized to be linked to prostaglandins. Berstad and coauthors (27) reported increased intraluminal concentrations of PGE_2 in response to intragastric administration of both high and low doses of aluminum hydroxide and aluminum hydroxide containing antacids. The increase in PGE_2 was greater with the high dose of aluminum hydroxide alone than when it was given in an antacid mixture together with magnesium hydroxide and calcium carbonate. Tarnawski and colleagues (28) reported increased mucus discharge in areas where aluminum hydroxide containing antacid crystals adhered to the mucosal surface. These aluminum hydroxide containing antacids induced an increase in hydrogen secretion, potassium and osmolality of gastric contents and increased luminal concentration and release of PGE_2 by 5-20 times ($p<0.01$) over controls. Many studies have shown that PGE_2 was effective in preventing the gastrointestinal blood loss induced by acetylsalicylic acid (aspirin) in healthy volunteers (29-30). Acetylsalicylic acid induced gastric bleeding was also decreased in the presence of PGE_2 in healthy volunteers (31-33).

Furthermore, several studies have shown that prostaglandins protect the gastric mucosal barrier by

tightening the mucosal barrier. They thereby prevented gastric alterations (increased fluxes of hydrogen, sodium, and potassium, decreased transmucosal electrical potential, and increased pepsin secretion) produced by intragastric administration of aspirin in both rats and dogs (34-36). The cytoprotection resulting from "tightening" of the gastric mucosal barrier may have decreased absorption of ^{51}Cr in the group receiving Maalox (aluminum hydroxide and magnesium hydroxide combination antacid) in our study.

Aspirin damages the gastric mucosa following oral administration in the non-ionized form (37). However, the underlying mechanism responsible for an increase in mucosal permeability and formation of hemorrhagic erosions remains unclear. A theoretical model proposes that gastric toxicity is due primarily to accumulation of drug anions in the surface mucosal cells. In the normally acidic gastric lumen, aspirin is predominantly un-ionized and therefore rapidly absorbed but on entering the neutral environment of the mucosal cells the drug becomes ionized and is trapped. It is possible that dissociation of the acid may disturb the internal osmotic stability and buffer system of the cell, while the high concentration of anions may interfere with intracellular metabolism (37, 38).

Clinical and physiological investigations have clearly shown that aspirin injures the gastric mucosa. Physiologically, the damage results in sharp increases in the movement of tissue electrolytes, larger molecules

(including DNA), and even epithelial cells into the gastric lumen. Changes in mucous, potential difference, and blood flow have also been associated with aspirin intake (37). Davenport has postulated the existence of a number of gastrointestinal barriers. These include barriers for electrolyte flux, protein loss, and red cell movement (39). Epithelial cells of the gastric mucosa, like other cells, have a lipid and protein layer penetrated by water-filled channels. This layer links adjacent cells by so-called tight junctions at their surface. Water, electrolytes, and water-soluble drugs such as glucose and urea can enter the mucosal surface through these "pores".

Fat-soluble compounds on the other hand, cross the membrane by dissolving in the lipid. Acetylsalicylic acid is relatively lipid-soluble in the un-ionized state, and at pH 1 can penetrate the gastric mucosa. Increased absorption of hydrogen ions follows, producing in turn greater mucosal damage. At the same time more sodium ions move into the gastric lumen. Alterations of mucosal permeability occur thereby allowing greater absorption of aspirin via a leaky gastric mucosal barrier (40).

Despite almost 100 years of widespread use, the mode of action of aspirin and several other OTC analgesics is not accepted unequivocally. Aspirin is a relatively potent inhibitor of prostaglandin synthesis and shows signs of ccumulation in inflamed tissues, the wall of the gastrointestinal tract, the kidney, liver, blood and bone

marrow. Hence, it has been assumed that inhibition of prostaglandin synthesis in these body compartments is the most important molecular mode of action (41-42). However, further study is needed.

In our study, absorption of ^{51}chromium was significantly higher in the aspirin group than in the vitamin C group. This increased absorption of ^{51}chromium in the aspirin group does not appear to be strictly pH related, because the pH of vitamin C was 2.76, while the pH of aspirin was 2.74. Furthermore, ^{51}chromium absorption and retention in the Bufferin group (pH 8.73) tended to be higher in blood ($p<0.08$) (Figure 1), and higher in liver and kidney ($p<0.11$) (Figure 3) than the vitamin C group. The pH of Bufferin (pH 8.73), Tums (pH 9.72) and Maalox (pH 8.39) was similar. Thus, the differences in absorption and retention can not be explained by pH alone. ^{51}Chromium absorption may be influenced by chelation or acetylation by aspirin or possibly by prostaglandin inhibition. Measurement of prostaglandins, plasma proteins, glucose, and salicylate metabolites would provide important information on the specific mechanisms involved in chromium absorption, retention and excretion.

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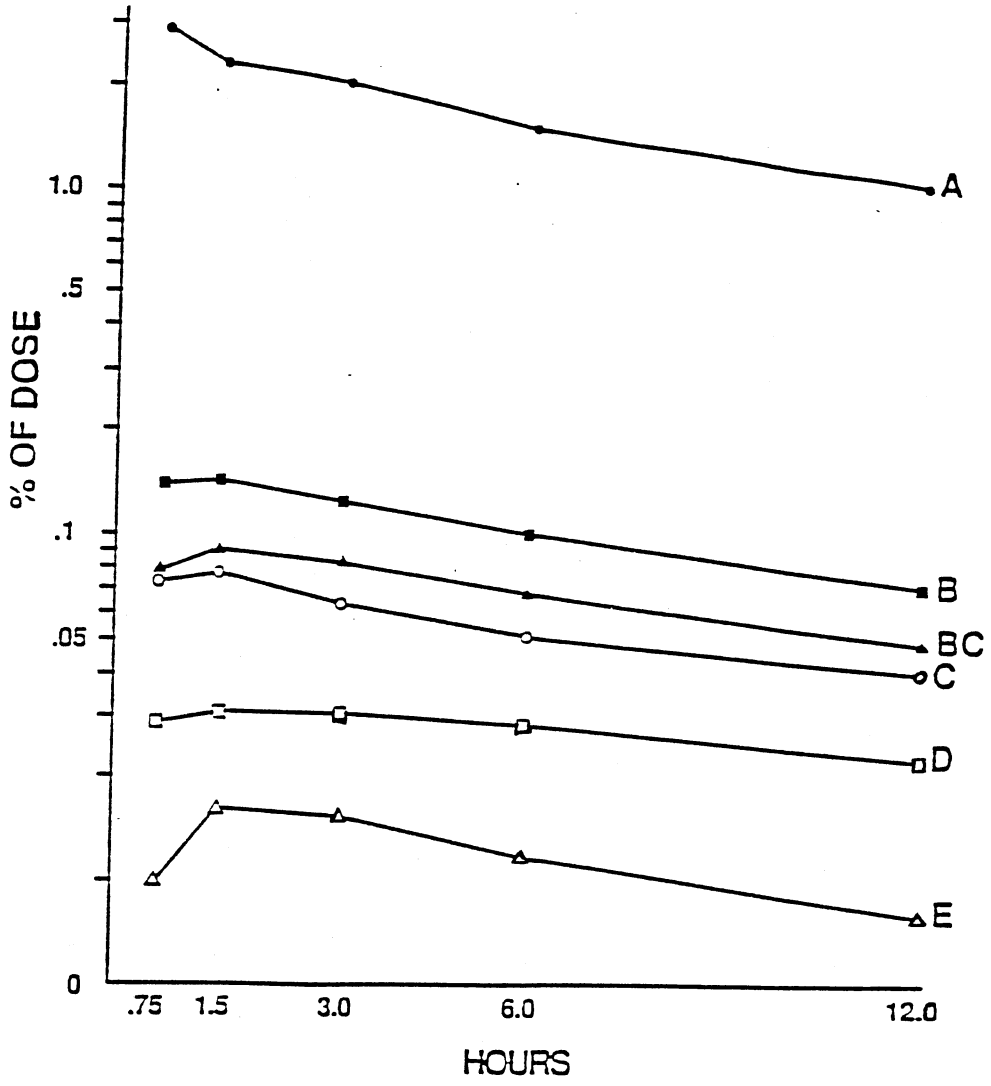
Figure 1. ^{51}Chromium in Blood[1]



[1] Means not sharing a common superscript are significantly different.

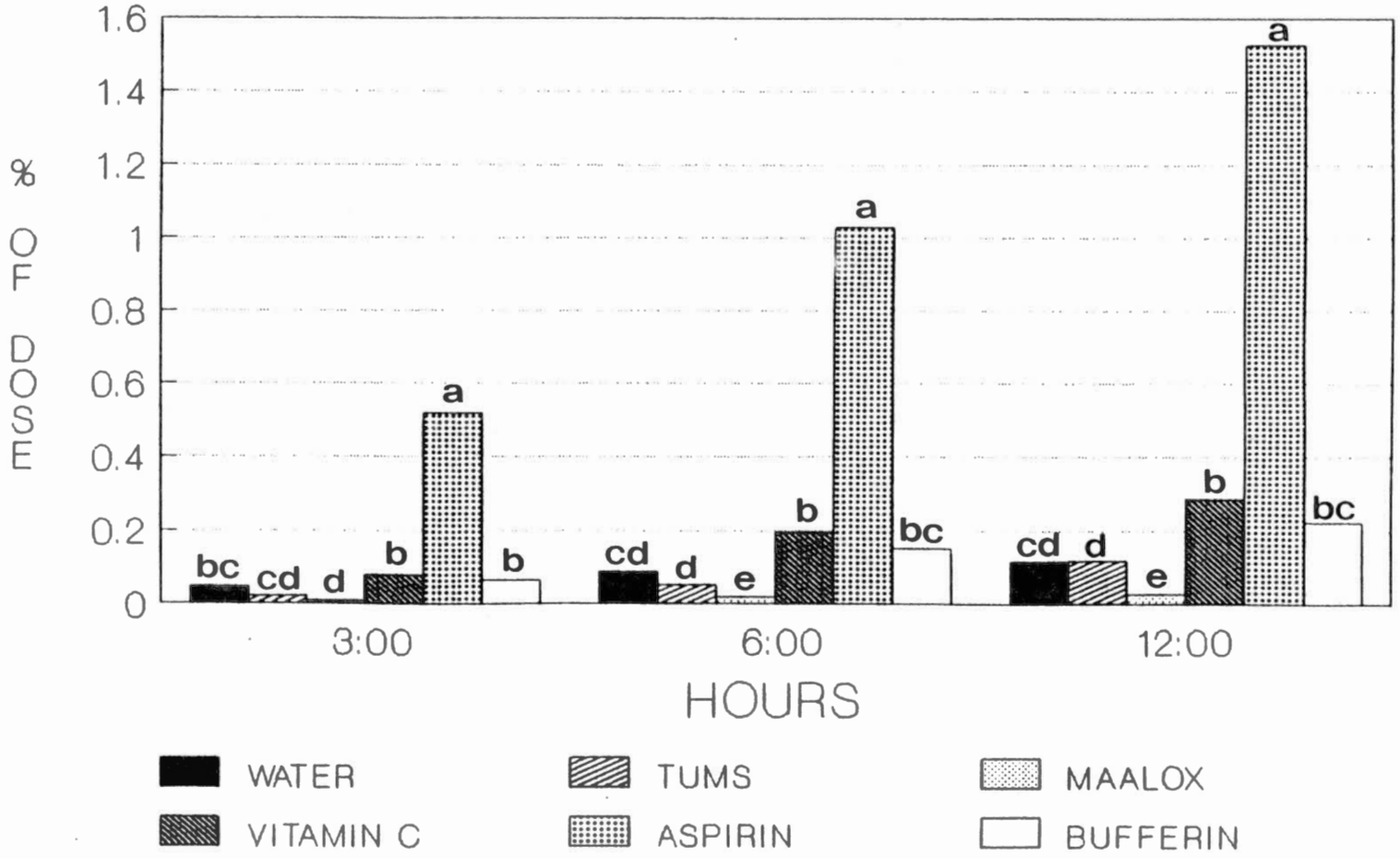


Figure 2. 51 Chromium in Urine

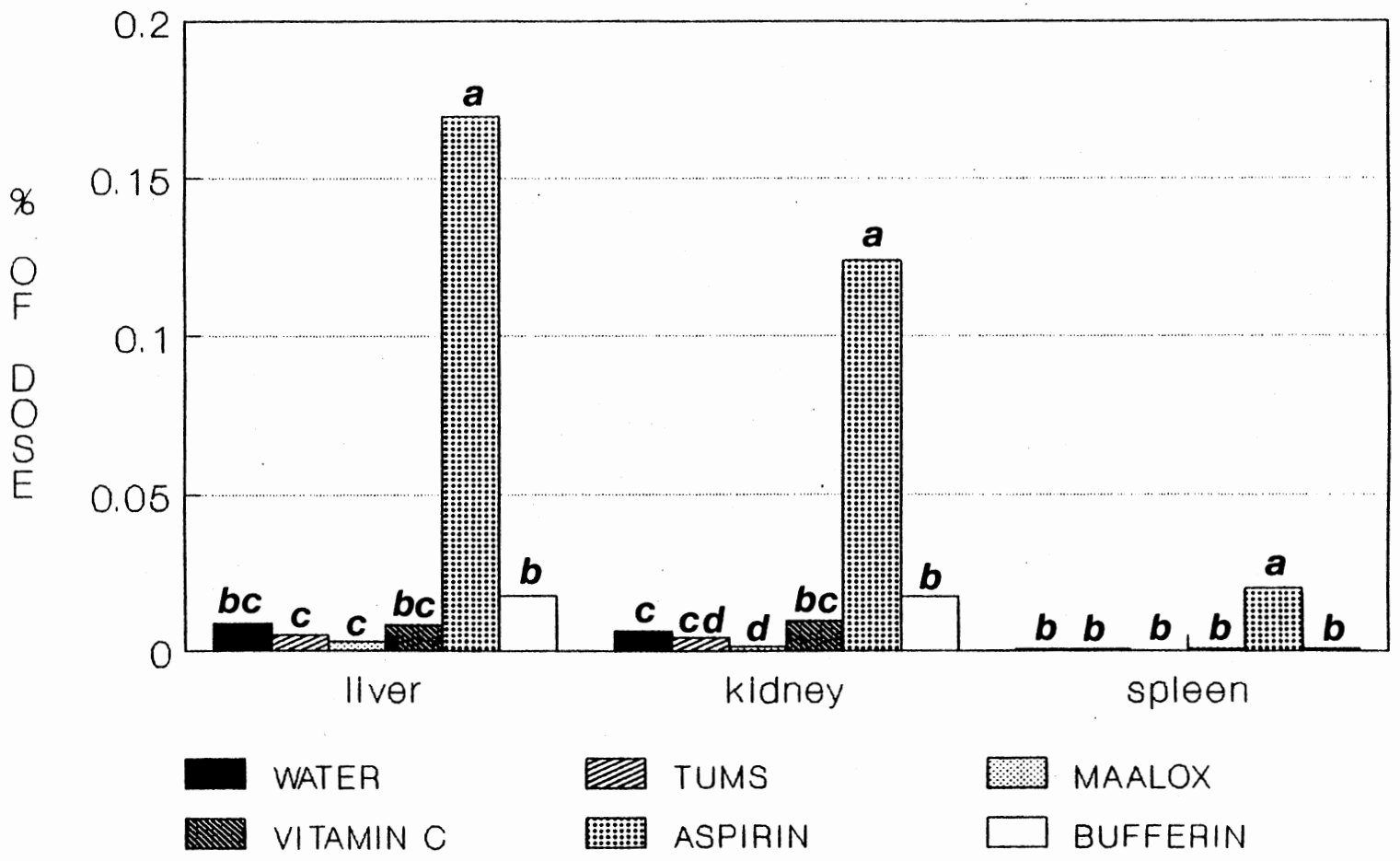


Figure 3. 51 Chromium In Tissue

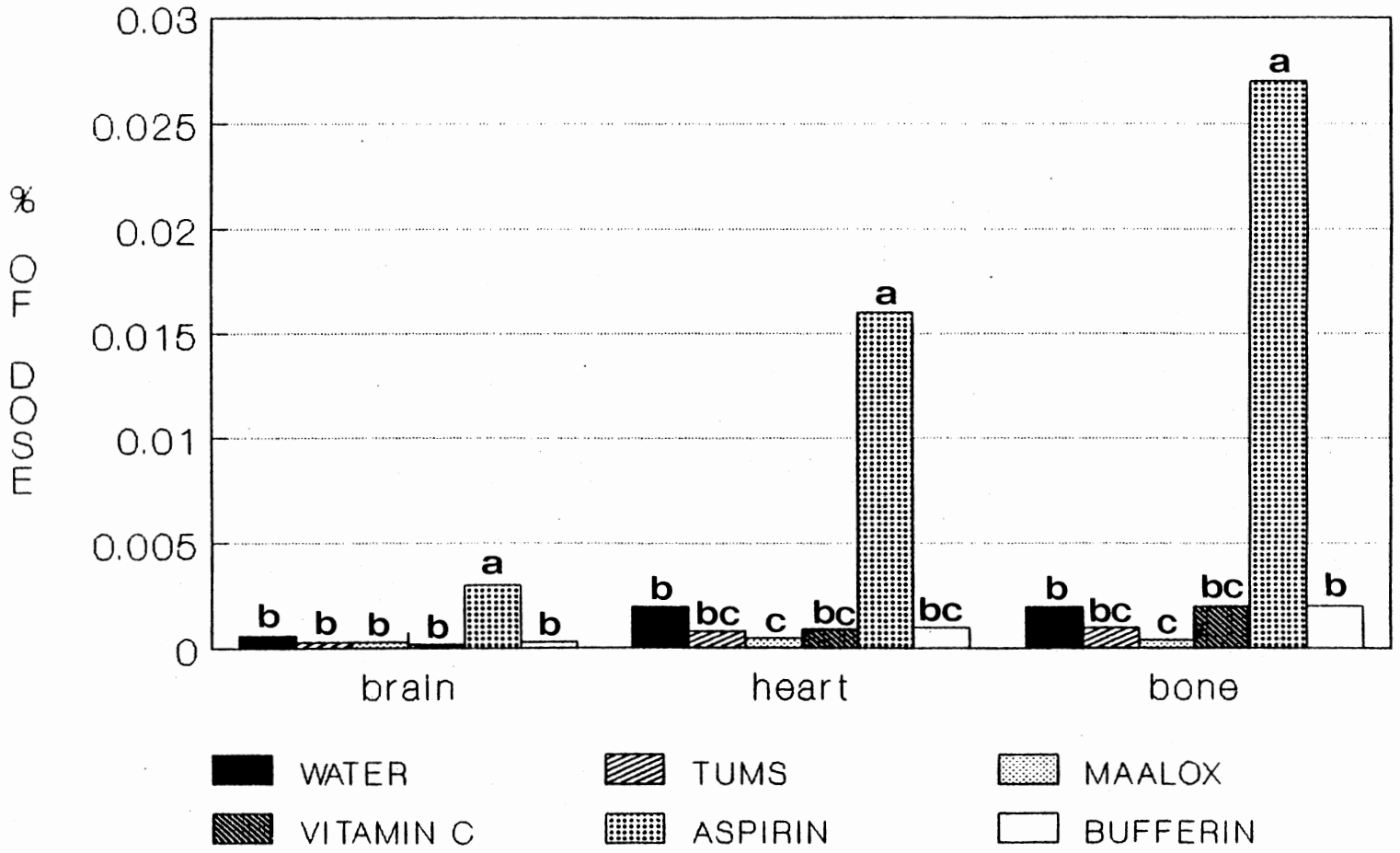


Figure 4. 51 Chromium In Tissue

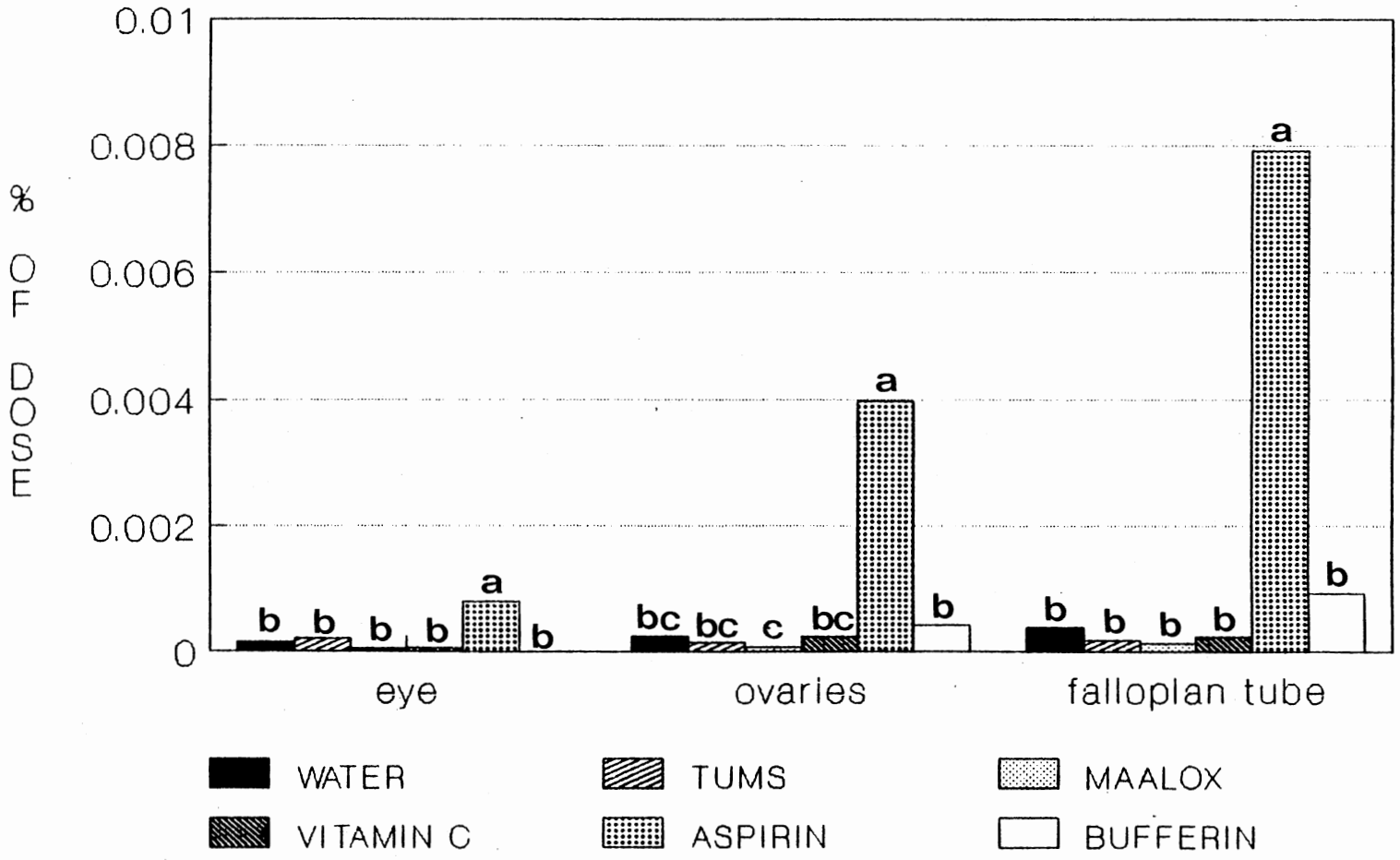


Figure 5. 51 Chromium in Tissue

CHAPTER IV

SUMMARY AND CONCLUSIONS

Summary

Forty-six female Sprague Dawley rats (mean weight 278±5 grams) were randomly assigned to six treatment groups. In addition to the control group given distilled water, groups were given Tums, Maalox, vitamin C, aspirin or Bufferin. After a twelve hour fast, the drugs were administered by gastric intubation followed immediately by an oral dose of $^{51}CrCl_3$. Blood, urine and tissues were sampled and counted in a gamma counter to assess ^{51}chromium chloride absorption, retention and excretion.

^{51}Chromium in blood, urine and tissues was higher ($p<0.0001$) in the aspirin group than in other groups. The group given Maalox had lower ($p<0.0001$) ^{51}chromium in blood, urine and tissues than the other groups. The Tums group was lower than all except the Maalox group. Groups dosed with water, vitamin C and Bufferin had values between aspirin and the two antacids.

Conclusions

The objective of the study was to determine if selected over-the-counter drugs (Tums, Maalox, vitamin C, aspirin or

Bufferin) alter absorption, retention or urinary excretion of ^{51}Cr from $^{51}CrCl_3$ in female rats. Based on the results of these analyses the following conclusions were reached.

Hypothesis

There will be no statistically significant differences in absorption, retention or excretion of ^{51}chromium from $^{51}CrCl_3$ due to a dose of distilled water, Tums, Maalox, vitamin C, aspirin or Bufferin.

The hypothesis was rejected. There were significant differences in absorption, retention and excretion of ^{51}chromium from $^{51}CrCl_3$ after dosing with Tums, Maalox, vitamin C, aspirin or Bufferin.

Recommendations

The following recommendations for future research were developed from this study. While the effects of single-dosing of over-the-counter drugs on chromium metabolism may be generalizable to infrequent self-medication for occasional pain or discomfort, long term studies with therapeutic dosing are needed to evaluate the effects of their chronic use on chromium metabolism. The measurement of prostaglandins may provide more insight into the possible mechanisms influencing the pharmacodynamics of drugs and their interactions with chromium. Salicylate measurement, creatine clearance, glucose and plasma protein measurements are all parameters worthy of investigation.

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APPENDIX

TABLE 1

Effects of Over-the-Counter Drugs on ^{51}Cr in Blood at Various Times after Dosing[1,2]

Drug	n	Time				
		45 min	1.5 hr	3 hr	6 hr	12 hr
		% of Dose				
Water	8	0.073±0.018^{b}	0.075±0.018^{b}	0.066±0.014^{b}	0.053±0.011^{bc}	0.041±0.009^{b}
Tums	9	0.029±0.006^{b}	0.030±0.006^{b}	0.031±0.005^{c}	0.029±0.005^{c}	0.023±0.004^{b}
Maalox	8	0.010±0.007^{c}	0.016±0.007^{c}	0.016±0.006^{d}	0.012±0.003^{d}	0.008±0.003^{c}
Vitamin C	8	0.079±0.023^{b}	0.090±0.024^{b}	0.086±0.023^{b}	0.071±0.019^{b}	0.050± 0.012^{b}
Aspirin	6	2.974±0.792^{a}	2.312±0.743^{a}	2.070±0.530^{a}	1.572±0.365^{a}	1.038± 0.215^{a}
Bufferin	7	0.142±0.052^{b}	0.143±0.055^{b}	0.128±0.050^{b}	0.105± 0.038^{b}	0.081±0.024^{b}

[1]Mean ± SEM.
[2]Means not sharing a common superscript are significantly different ($p<0.05$).

TABLE 2

Effects of Over-the-Counter Drugs on Total ^{51}Cr in Urine at 3, 6, and 12 Hours after Dosing[1,2]

		Time		
Drug	n	3 hr	6 hr	12 hr
		% of Dose		
Water	8	0.045 ± 0.012^{bc}	0.089 ± 0.123^{cd}	0.119 ± 0.028^{cd}
Tums	9	0.020 ± 0.005^{cd}	0.052 ± 0.010^{d}	0.119 ± 0.042^{d}
Maalox	8	0.008 ± 0.003^{d}	0.018 ± 0.006^{e}	0.027 ± 0.009^{e}
Vitamin C	8	0.078 ± 0.017^{b}	0.195 ± 0.042^{b}	0.286 ± 0.055^{b}
Aspirin	6	0.518 ± 0.171^{a}	1.029 ± 0.317^{a}	1.528 ± 0.357^{a}
Bufferin	7	0.064 ± 0.019^{b}	0.152 ± 0.033^{bc}	0.221 ± 0.040^{bc}

[1]Mean ± SEM.
[2]Means not sharing a common superscript are significantly different ($p<0.05$).

TABLE 3

Effects of Over-the-Counter Drugs on ^{51}Cr in Tissues 12 Hours after Dosing[1,2]

Drug	n	Liver	Kidney	Spleen
			% of Dose	
Water	8	0.0089±0.0018^{bc}	0.0063±0.0010^{c}	0.0008±0.0003^{b}
Tums	9	0.0051±0.0009^{c}	0.0045±0.0006^{cd}	0.0007±0.0001^{b}
Maalox	8	0.0030±0.0011^{c}	0.0015±0.0006^{d}	0.0004±0.0001^{b}
Vitamin C	8	0.0083±0.0020^{bc}	0.0097±0.0028^{bc}	0.0008±0.0002^{b}
Aspirin	6	0.1697±0.0358^{a}	0.1240±0.0214^{a}	0.0199±0.0060^{a}
Bufferin	7	0.0176±0.0042^{b}	0.0174±0.0046^{b}	0.0009±0.0002^{b}

[1]Mean ± SEM.
[2]Means not sharing a common superscript are significantly different ($p<0.05$).

TABLE 4

Effects of Over-the-Counter Drugs on ^{51}Cr in Tissues
12 Hours after Dosing[1,2]

Drug	n	Brain	Heart	Bone
		% Dose	% Dose	% Dose/g
Water	8	0.0006 ± 0.0003^{b}	0.0018 ± 0.0004^{b}	0.0017 ± 0.0004^{b}
Tums	9	0.0003 ± 0.0001^{b}	0.0008 ± 0.0002^{bc}	0.0010 ± 0.0002^{bc}
Maalox	8	0.0003 ± 0.0001^{b}	0.0005 ± 0.0002^{c}	0.0004 ± 0.0001^{c}
Vitamin C	8	0.0002 ± 0.0001^{b}	0.0009 ± 0.0003^{bc}	0.0017 ± 0.0004^{bc}
Aspirin	6	0.0025 ± 0.0004^{a}	0.0162 ± 0.0026^{a}	0.0265 ± 0.0050^{a}
Bufferin	7	0.0003 ± 0.0001^{b}	0.0010 ± 0.0003^{bc}	0.0022 ± 0.0006^{b}

[1]Mean ± SEM.
[2]Means not sharing a common superscript are significantly different ($p<0.05$).

TABLE 5

Effects of Over-the-Counter Drugs on ^{51}Cr in Tissues
12 Hours after Dosing[1,2]

Drug	n	Eye	Ovaries	Fallopian Tube
			% Dose	
Water	8	0.00015±0.00006^{b}	0.00026±0.00005^{bc}	0.00040±0.00007^{b}
Tums	9	0.00021±0.00010^{b}	0.00015±0.00006^{bc}	0.00019±0.00004^{b}
Maalox	8	0.00005±0.00003^{b}	0.00008±0.00004^{c}	0.00014±0.00005^{b}
Vitamin C	8	0.00006±0.00003^{b}	0.00024±0.00010^{bc}	0.00025±0.00008^{b}
Aspirin	6	0.00079±0.00013^{a}	0.00397±0.00085^{a}	0.00791±0.00235^{a}
Bufferin	7	0.00002±0.00002^{b}	0.00042±0.00013^{b}	0.00093±0.00054^{b}

[1]Mean ± SEM.
[2]Means not sharing a common superscript are significantly different ($p<0.05$).

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