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RESEARCH ARTICLES

GI Motor Inhibition Associated with Acute Exposure to Methyl Methacrylate Vapor

MARTIN F. TANSY ˣ, JOHN S. MARTIN, SEROUYA BENHAIM, WENDELL E. LANDIN, and FRANK M. KENDALL

Abstract □ A mixture of monomeric methyl methacrylate vapor in air was delivered into the breathing air of chloralose–urethan anesthetized dogs. Fixed length exposures to 2000-ppm doses of the vapor resulted in a transient drop in arterial blood pressure and a marked inhibition of ongoing GI motor activities. Motor inhibition always continued for a variable time (~10–15 min) subsequent to the cessation of methyl methacrylate vapor administration. This inhibitory response was not blocked by bilateral vagotomy, spinal transection, splanchnectomy, or the intravenous administration of tetraethylammonium chloride. Another series of experiments determined that the administration of blood from a dog receiving methyl methacrylate vapor produced GI motor inhibition in another dog not connected to the experimental gas mixture. Therefore, it is concluded that, aside from any reflex effects produced, methyl methacrylate vapor in sufficient concentration probably exerts a direct inhibitory effect upon GI smooth muscle that is mediated by the cardiopulmonary systems.

Keyphrases □ Methyl methacrylate monomeric vapor—pulmonary exposure, effects on GI motor activities, dogs □ GI motor activities—effect of pulmonary exposure to monomeric methyl methacrylate vapor, dogs □ Toxicity—monomeric methyl methacrylate vapor, pulmonary exposure, effects on GI motor activities, dogs

Published experiments (1) from this laboratory previously demonstrated that short exposures of conscious rats to relatively high concentrations of methyl methacrylate vapor in air were associated with rapid declines in the amplitudes of gastric pressure events. These pressure events gradually reestablished normal patterns within 4 min of cessation of methyl methacrylate vapor exposures for 5–10 min. A similar observation was made with a single human subject during an exposure comparable to that received occupationally (1).

The second objective of these acute motility experiments (1) was to determine a possible reflex mechanism that could reasonably be inferred to mediate the inhibition of gastric motor activity associated with the acute exposure of the rat to methyl methacrylate vapor. However, the results were equivocal because cervical vagotomy does not define a reflex originating in the pulmonary apparatus having its afferent and efferent limbs in the vagus and subdiaphragmatic vagotomy cannot be performed as surely in the rat. For this surgical reason, the chloralose–urethan anesthetized dog was employed as the experimental animal after satisfying the requirement that a similar inhibitory response can be produced. Therefore, the experimental observations were extended to another species.

EXPERIMENTAL

Animals and General Procedure—Twelve adult mongrel dogs of both sexes were equilibrated for at least 3 days in the local animal facility prior to use. All experiments were undertaken after the animals had been fasted overnight but with water allowed *ad libitum*. All dogs were individually titrated to a surgical plane of anesthesia by the intravenous administration of a mixture of α-chloralose (5%, dissolved in polyethylene glycol 200) and urethan (50% in 0.9% saline). Further injections of the chloralose–urethan mixture were given when necessary.

Surgical and Recording Procedures—The femoral artery was cannulated to permit the continuous measurement of systemic blood pressure, and the ipsilateral vein was cannulated to permit administration of tetraethylammonium chloride[1] and fluids. Each animal was tracheostomized to permit monitoring of respiration, artificial respiration, and administration of methyl methacrylate vapor. On occasion, a pneumograph was used to record respiratory movements.

A midline laparotomy was then performed. Recording balloons were inserted *via* the oral route for gastric recording and retrograde *via* a stab wound in the ileum for small intestinal recording. Polygraphic control tracings were obtained before and at stated intervals after the physical and chemical stimulatory procedures in each group of dogs. In all in-

[1] Etamon, Parke, Davis.

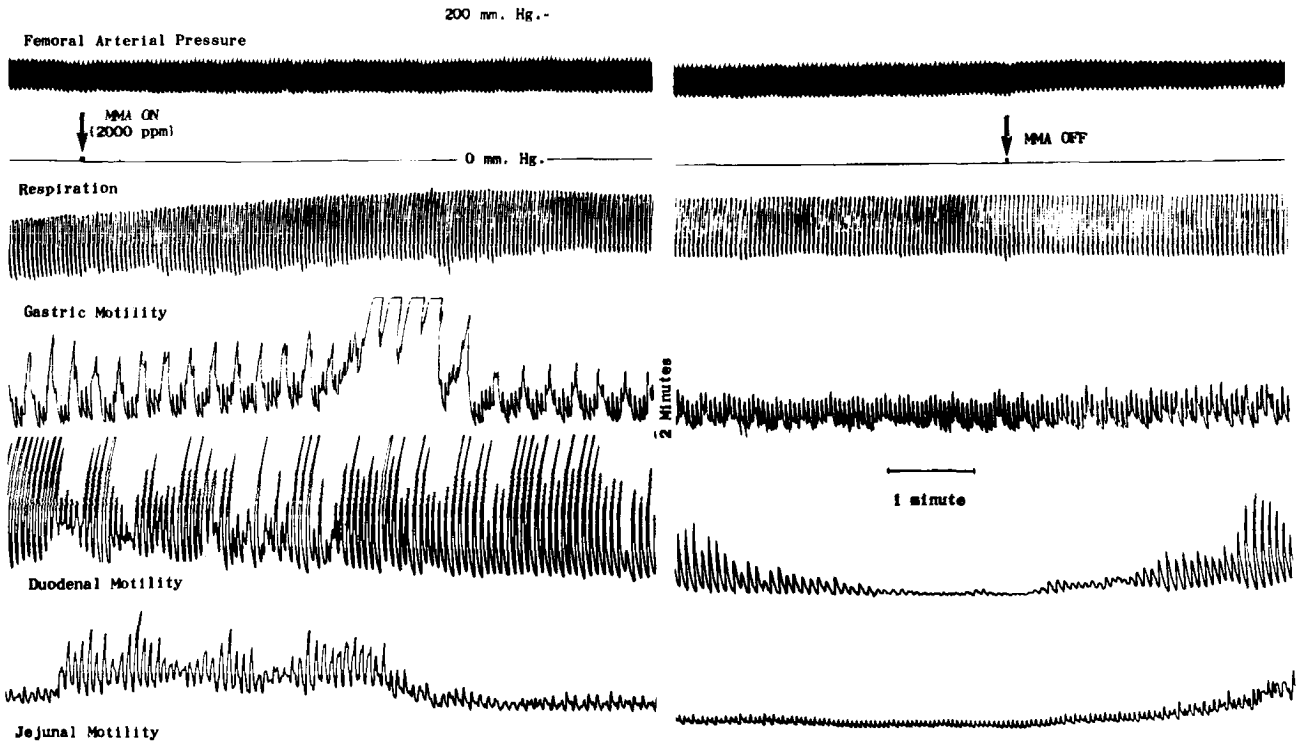

Figure 1—*Polygram of physiological parameters observed during the acute exposure of a chloralose–urethan anesthetized dog to methyl methacrylate (MMA) vapor at 2000 ppm in air. A slight, transient decline in arterial blood pressure was observed. Respiratory rate and relative tidal volume (as measured by a pneumograph) were substantially unchanged. Gastric pressure indications suggest an initial augmentation of active contractile activity followed by a decline in the active component with little effect upon tonus. Duodenal motor activity suggests a drastic decline in active contractile activity as well as a reduction in tonus. The jejunum fortuitously began a bout of contractile activity just before the exposure commenced. Both the active and tonus components of this activity were inhibited during exposure.*

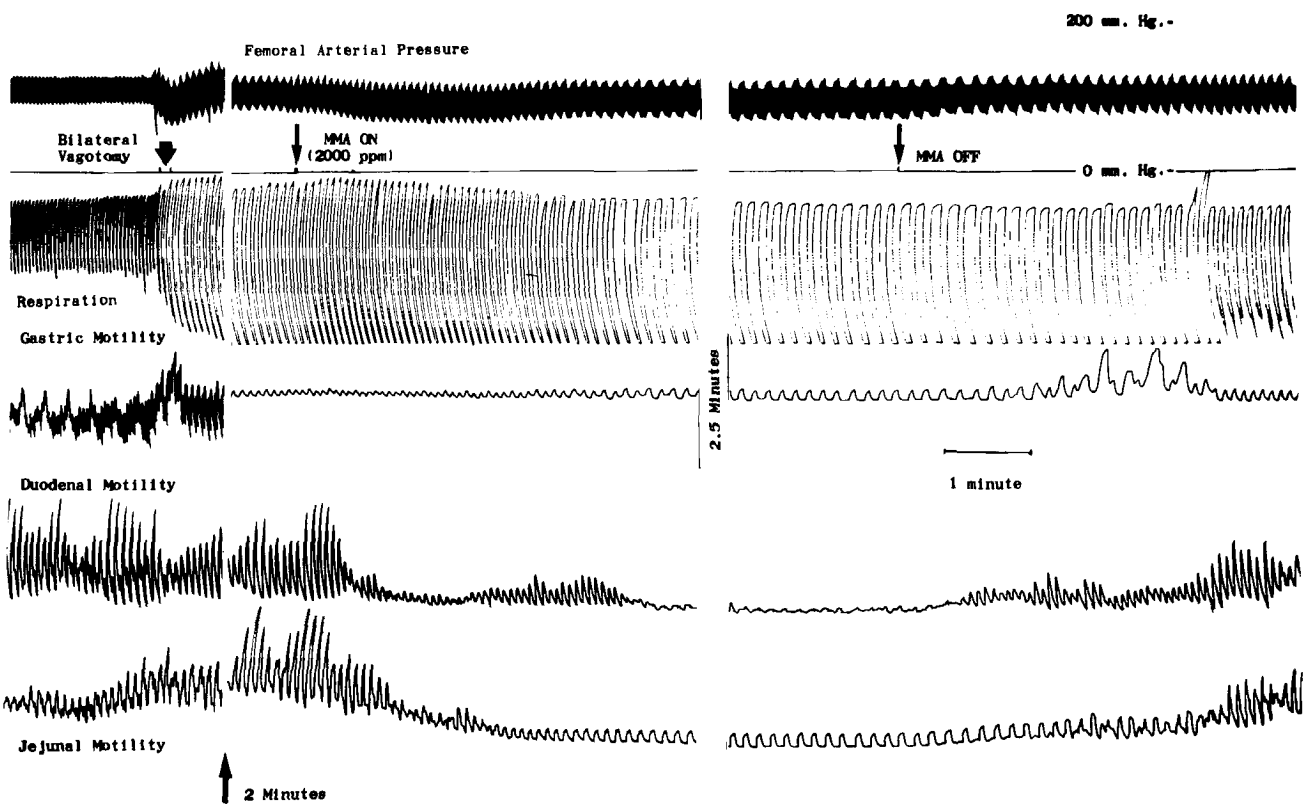

Figure 2—*Continuation of the experiment depicted in Fig. 1. Both vagi were severed, and the gas exposure was repeated. Gastric, duodenal, and jejunal motor activities continued to be inhibited during exposure. The transient depression in arterial blood pressure was more evident in magnitude and duration during the exposure to 2000 ppm of methyl methacrylate (MMA) vapor in air.*

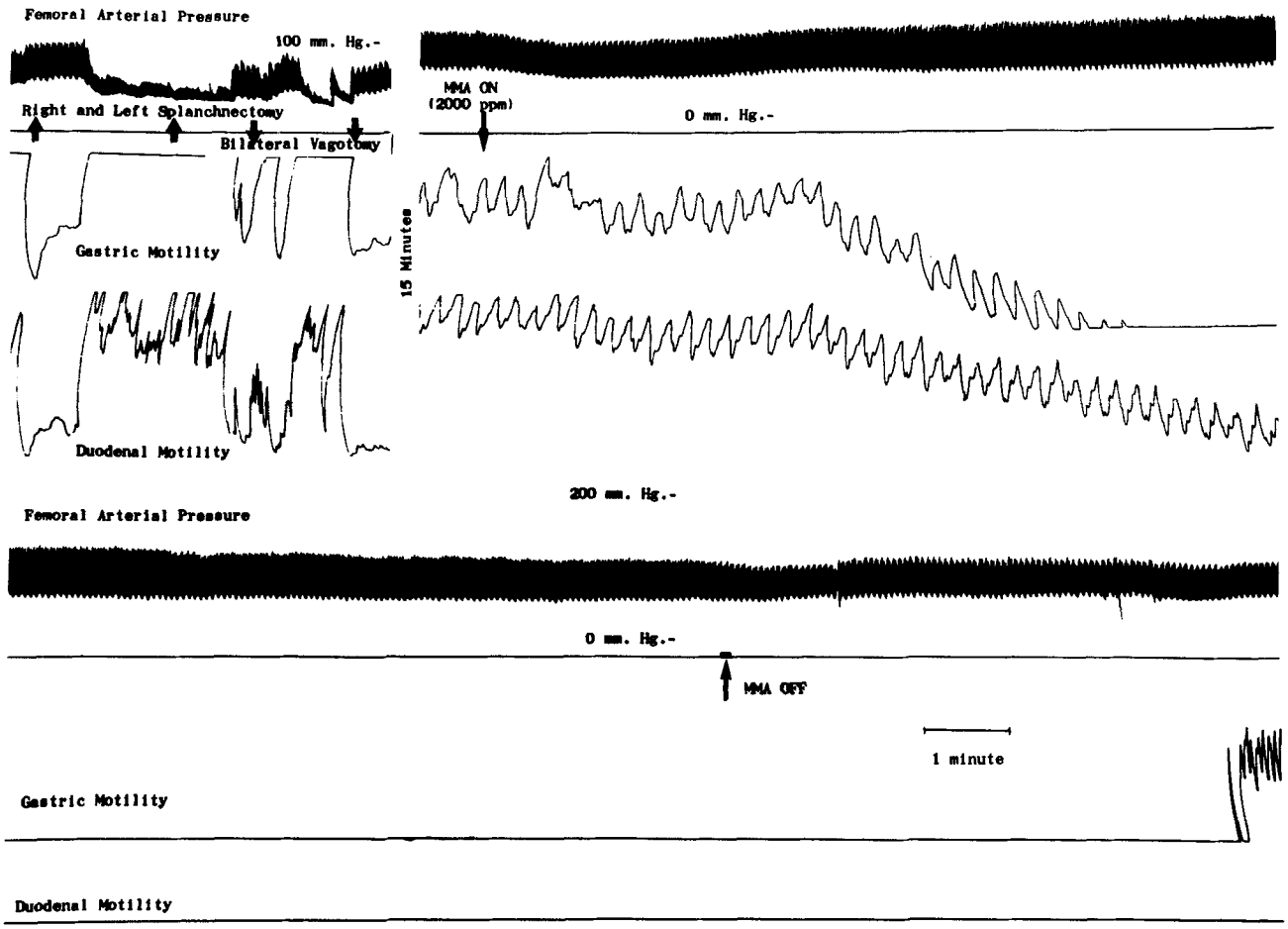

Figure 3—*Effects of acute exposure to 2000 ppm of methyl methacrylate (MMA) vapor in air following bilateral vagotomy and splanchnectomy (top panel) in a chloralose–urethan anesthetized dog. The active and tonus components of gastric and duodenal motor activities were severely inhibited (top of lower panels). Arterial blood pressure was transiently affected.*

stances, the designation of intestinal pressure records as signifying a particular type of motility response is justified on the basis of a visual observation that such a response occurred concurrently with the recorded pressure events.

Vapor Administration and Analyses—The methyl methacrylate monomer[2] used contained 10 ppm of the monoethyl ether of hydroquinone as an inhibitor. During all methyl methacrylate vapor administrations, the dogs were ventilated at a fixed minute volume of 4–6 liters. Pilot experiments were performed to determine empirically a rate of methyl methacrylate vapor introduction that would consistently produce the motor effects desired. Once this rate was determined, samples of the resulting gas mixture were analyzed by GLC[3] and the average measured concentration was assumed to be constant throughout the balance of the experiments. In view of the minute volume, it was assumed that the methyl methacrylate vapor rapidly disappeared from the respirator system when the supply of methyl methacrylate vapor was turned off.

RESULTS AND DISCUSSION

For all practical purposes, each animal was used for at least one control run prior to the performance of any procedure not already outlined. Figure 1 represents a typical polygram produced by such a run. Gastric antral pressure amplitudes became depressed during exposure. In all cases, a transient but vigorous bout of gastric contraction appeared shortly after the first introduction of methyl methacrylate vapor. This effect never occurred more than once. Gastric antral pressure activity became depressed during exposure and gradually approached control values after cessation of exposure. Small intestinal pressure amplitudes also were depressed.

The rate of onset of inhibition was not apparently a necessary function of the observed organs. In this polygram, it can be seen that the duodenum exhibited a higher degree of contractile activity during the control period. In this case, degradation of duodenal activity followed a longer time course than that of jejunum activity, which became quiescent much sooner. The latency of the inhibitory response was generally proportional to the degree of pressure activity produced by the organ prior to administration of methyl methacrylate vapor.

Figure 2 shows the responses of the previous animal to methyl methacrylate vapor following subdiaphragmatic vagotomy. A short administration of methyl methacrylate vapor quickly reduced intestinal pressure activity, which remained depressed for the duration of the exposure. In this particular experiment, the motor activity of the gastric antrum had not recovered from the transient effects of vagotomy by the time that this exposure was performed. In this record, only the onset of the return of antral motor activity is apparent. Subsequently, this activity returned and was inhibited by further methyl methacrylate exposures. There appeared to be a transient fall in arterial blood pressure in the vagotomized animal following the start of methyl methacrylate vapor administration.

Figure 3 depicts polygrams obtained from a mechanically ventilated, splanchnectomized, vagectomized dog anesthetized with chloralose–urethan. These recordings depict the time course of arterial blood pressure and gastric and duodenal motor activities. The left portion of the top panel shows the artifacts produced by sectioning of the splanchnic nerves and vagi. Methyl methacrylate vapor was introduced into the air supply, and motor activities were abruptly reduced, primarily in terms of loss of tonus. Contractile events were not seen because the pens bottomed in the channel stops. Within 7–8 min after cessation of exposure, gastric tone abruptly reappeared.

The polygrams shown in Fig. 4 were obtained as a continuation of the

[2] Rohm and Haas.

[3] The column was 1.5-m × 0.3-cm (5-ft × 0.125-in.) o.d. stainless steel, packed with 20% Carbowax 20M, coated onto 80–100-mesh Chromosorb W. The chromatographic conditions were: column oven (starting) temperature, 100°; injection port temperature, 200°; detector temperature, 200°; helium pressure, 68 psi; helium flow, 30 ml/min; hydrogen pressure, 20 psi; air pressure, 20 psi; attenuation, 32×10^{-11}; recorder sensitivity, 1 mv; and sample size, 1 ml.

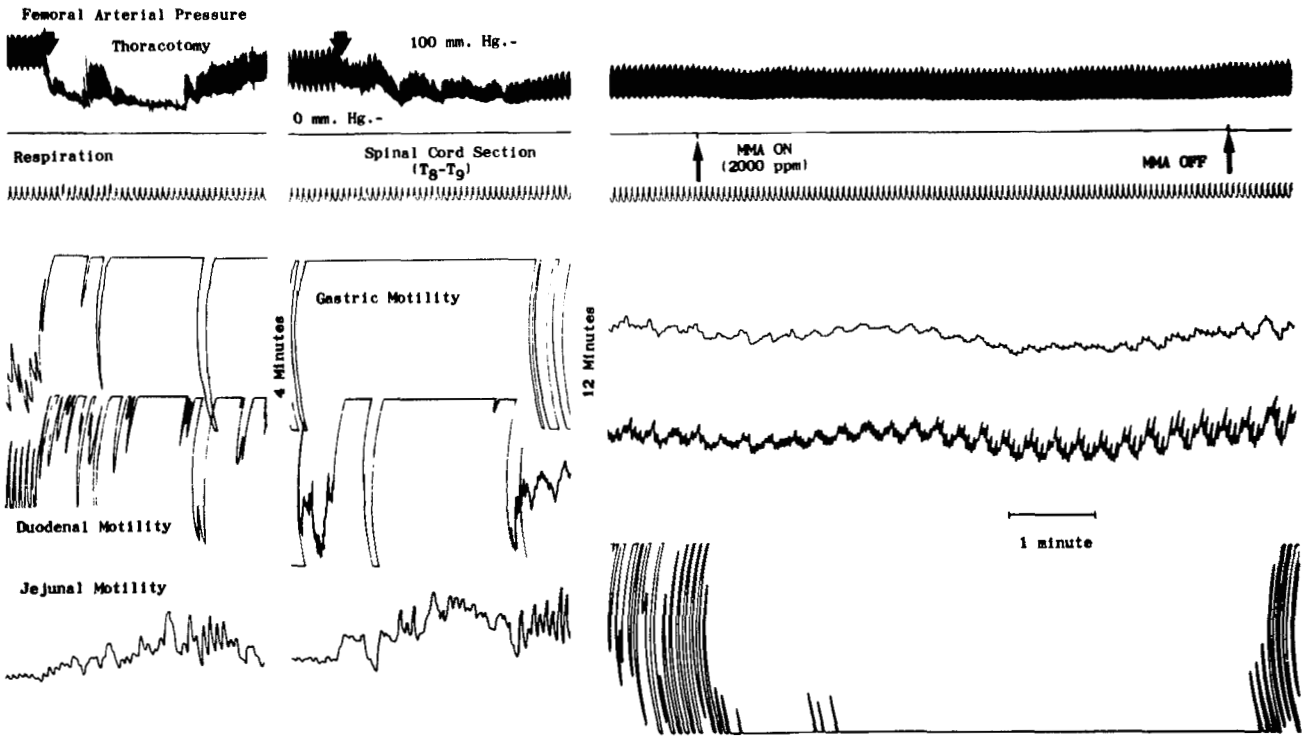

Figure 4—*Continuation of the experiment depicted in Fig. 3. Following recovery from the previous exposure, the dog was ventilated mechanically, a thoracotomy was performed, and the spinal cord was severed at the T_8–T_9 level. Tonus components of gastric and duodenal motor activities were slightly depressed. No remarkable changes in active contractile activity were apparent, because there was very little in evidence at the start of exposure. In contrast, the high amplitude jejunal activity present was abruptly abolished and spontaneously restored at the cessation of vapor exposure. A slight depressor effect on arterial blood pressure was seen.*

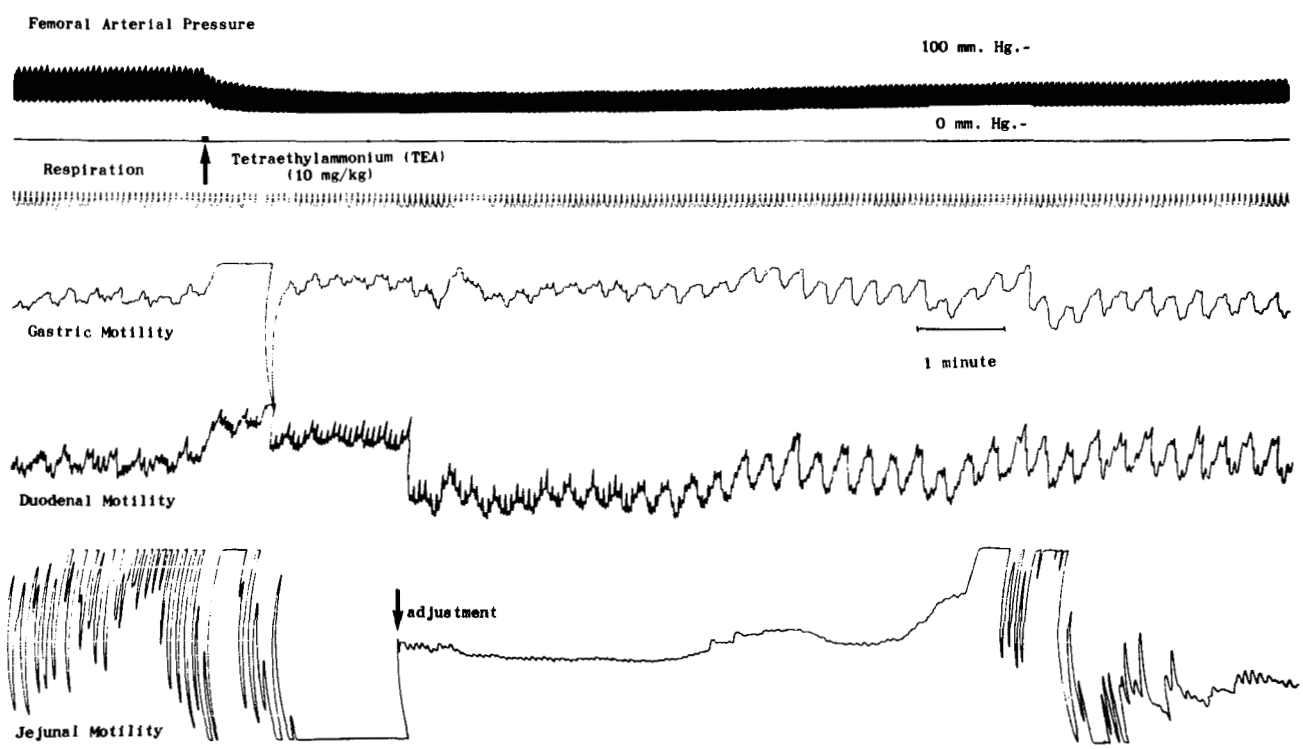

Figure 5—*Continuation of the experiment depicted in Figs. 3 and 4 following recovery from the previous exposure with a dog that has been bilaterally vagotomized, splanchnectomized, and spinally transected. Administration of the ganglionic blocking agent tetraethylammonium chloride (10 mg/kg) was associated with a decline in arterial mean and pulse pressures, a transient decline in duodenal active and tonus contractile components, and little effect upon gastric pressure activity. Jejunal contractile activity was inhibited. The baseline for jejunal pressure activity was reset to determine the effects of tetraethylammonium chloride on the active component.*

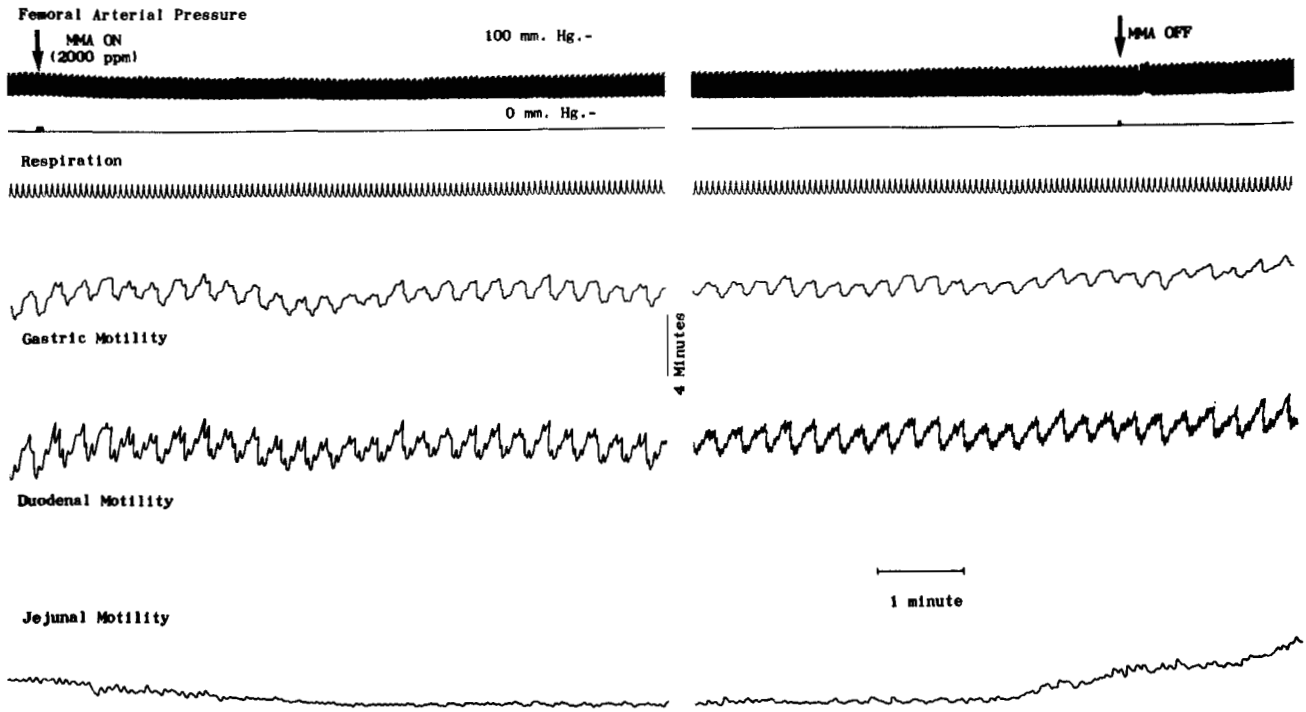

Figure 6—*Continuation of the experiment depicted in Figs. 3–5 following a recovery period from the previous procedures. At this point, reexposure to 2000 ppm of methyl methacrylate (MMA) vapor in air resulted in a slight decline in mean arterial blood pressure and a definite reduction in jejunal tonus.*

observations made during the experiment depicted in Fig. 3. In this record, relative respiratory motion and jejunal motor activities are included. The left and center panels depict the artifacts produced by retraction of the open chest and transection of the spinal cord between T_8 and T_9. During methyl methacrylate administration, gastric antral and duodenal motor activities were only slightly affected but jejunal tonus was drastically reduced.

Further observations were then conducted utilizing the by now surgically denervated viscera. The polygram in Fig. 5 shows the observed effects of tetraethylammonium chloride administration, which produced

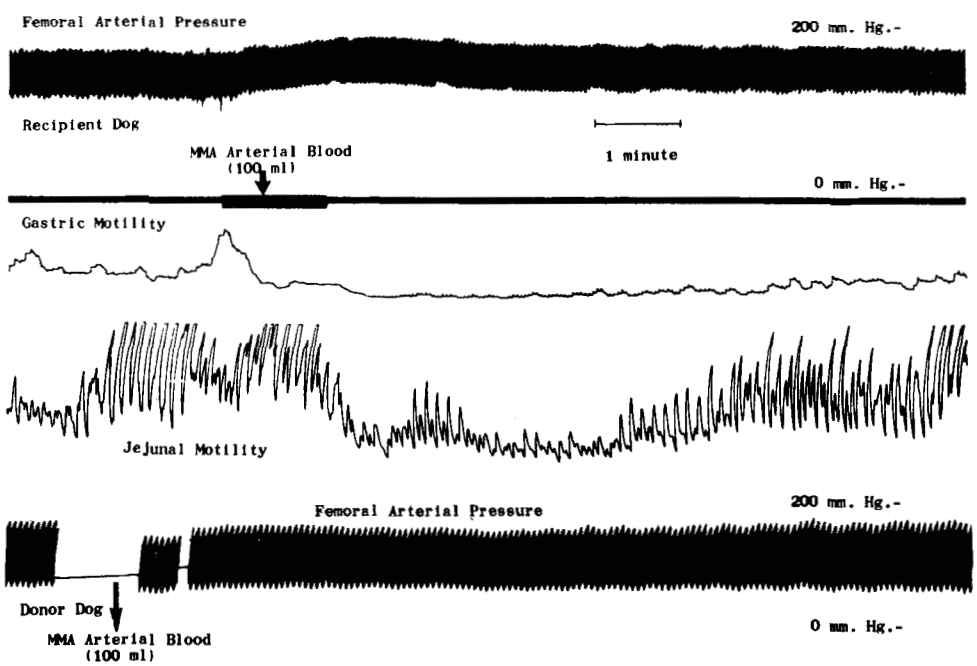

Figure 7—*Parallel polygrams obtained from chloralose–urethan anesthetized dogs. The donor dog (lower trace) was continuously exposed to 2000 ppm of methyl methacrylate (MMA) vapor in air for about 1 hr before these records were made. Arterial blood (100 ml) was obtained from the arterial pressure cannula of the exposed dog and rapidly infused into the femoral vein of the unexposed recipient dog (top traces). Gastric tonus of the recipient was depressed, but no inference can be drawn concerning an effect upon the active component of gastric activity which was not present at this time. The active and tonic components of jejunal activity were both depressed transiently in the recipient. The increase in mean arterial blood pressure of the recipient was most likely due to the hypervolemia produced by the infusion of 100 ml of whole blood, which would tend to obscure any transient decline due to the methyl methacrylate content of the donor blood.*

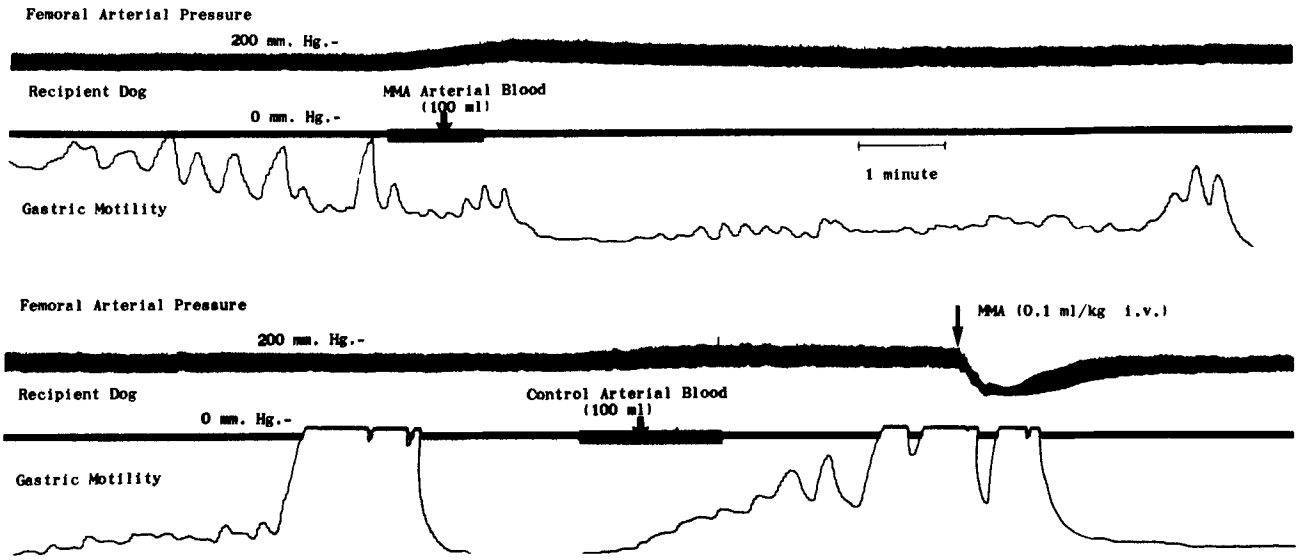

Figure 8—*Gastric contractile activity and arterial blood pressure events produced in a chloralose–urethan anesthetized dog following the infusion of 100 ml of whole blood from a donor dog (continuation of the experiment depicted in Fig. 7). In the top traces, the active and tonic gastric contractile activity of the recipient dog were depressed when 100 ml of whole blood, obtained during the exposure to 2000 ppm of methyl methacrylate (MMA) vapor in air, was infused via a femoral vein. The same experiment was repeated in the lower traces, where 100 ml of donor blood, obtained prior to methyl methacrylate exposure, was infused into the venous system of the recipient. Gastric contractile activity appeared to be normal following the infusion of blood from the donor prior to methyl methacrylate exposure, but recipient gastric motor activity was depressed following infusion from the methyl methacrylate exposed donor. At the end of the lower trace, the reactivity of the recipient was verified by the results of an intravenous administration of 0.1 mg/kg of the methyl methacrylate monomer. Gastric contractile activity was abolished and femoral arterial blood pressure was sharply, but transiently, affected.*

a transient fall in duodenal tonus and jejunal tonus and contractile activity. In this recording, the baseline of the jejunal pressure channel was reset to permit observation of the resulting motor activity, which was minimal.

Figure 6, a continuation of the record of Fig. 5, shows that the administration of methyl methacrylate vapor following ganglionic blockade with tetraethylammonium chloride was principally associated with a further depression of jejunal tonus and the by now minimal jejunal contractile activity. Jejunal tonus began to appear prior to the cessation of methyl methacrylate vapor administration.

A series of observations were then conducted simultaneously in real time utilizing four chloralose–urethan anesthetized dogs. These dogs had been subjected to identical surgical procedures: tracheostomies, arterial and venous cannulation, gastric antral recording balloons (oral route), and duodenal recording balloons (retrograde from the ileum). The purpose of these observations was to test the hypothesis that the motor effects associated with methyl methacrylate vapor administration could not be mediated in part by the circulation. Accordingly, methyl methacrylate vapor was only administered to one of each pair of dogs, and an arterial blood sample from the exposed (donor) dog was infused into the femoral vein of the nonexposed (recipient) dog. During these procedures, the monitored parameters were recorded graphically upon the same strip chart.

Figure 7 shows the time course of events in the recipient (top traces) and the donor (lower trace only) during these experiments. During the span of this record, the donor dog was continuously exposed to 2000 ppm of methyl methacrylate vapor *via* the breathing system. The top traces show that the slow infusion of 100 ml of donor blood resulted in a decrease in gastric and duodenal tonus and contractile activity. These activities gradually returned to control levels.

Figure 8 shows a continuation of the observations of the gastric antral activity of the recipient dog. Antral activity and tonus were reduced following intravenous administration of another sample of exposed donor blood (top traces). The lower traces show that recipient gastric activity was unchanged when an equal volume of donor blood, drawn during the control period prior to methyl methacrylate exposure, was infused.

Cardiovascular activity was monitored on a routine basis to indicate the general viability of the preparation and the responsiveness following certain procedures and as a general indication of cardiovascular toxicity. The time rate of the GI motor phenomena is unfortunately too low to permit adequate recording of faster cardiovascular phenomena without producing records of unusable length. As a result, the cardiovascular data are unsuitable for acquiring data for dynamic analysis. However, the records do show that direct administration of methyl methacrylate produced a decreased pulse pressure and probably a reflex tachycardia. These effects could be accounted for by two possible mechanisms: a direct toxic increase in arterial compliance and a direct toxic decrease in myocardial contractility. If, indeed, the general toxic effect of this agent resides in an inhibition of active contractile force, a further examination of the cardiovascular effects appears to be warranted.

The remainder of the foregoing data may be interpreted as follows. The acute studies indicated that the administration of methyl methacrylate is associated with a depression of tonus and contractile activity of the canine gastric antrum and proximal small bowel. Regardless of the presence or absence of visceral innervation, this effect had a latency on the order of 10 min when the agent was administered in vapor form. This latency was very short when either blood from an exposed dog or liquid methyl methacrylate was introduced intravenously. Although it was not included previously, a short latency was observed when the agent was administered intravenously to a surgically and chemically denervated preparation. Thus, the short latency might be indicative of a reflex response. However, the manifestation of the same effect in the denervated preparation, while not excluding the possibility that some reflex effects are produced, makes a reflex explanation for the observed response unlikely.

Inasmuch as this laboratory (2) and others (3) have observed that the monomer vapor depresses the spontaneous motor activity of intestinal strips *in vitro*, it may be concluded that methyl methacrylate vapor probably exerts a direct inhibitory effect upon GI smooth muscle and that the cardiopulmonary system is capable of mediating this effect when exposure is by inhalation.

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[x] To whom inquiries should be directed.

Disposition of Sulfonamides in Food-Producing Animals IV: Pharmacokinetics of Sulfamethazine in Cattle following Administration of an Intravenous Dose and Three Oral Dosage Forms

RICHARD F. BEVILL [*x], LEWIS W. DITTERT [‡], and DAVID W. A. BOURNE [‡]

Abstract □ The plasma and urine data obtained following intravenous administration of sulfamethazine to cattle were fit to a one-compartment pharmacokinetic model with a half-life of elimination of 9 hr and a volume of distribution of 0.35 liter/kg. Sulfamethazine was eliminated by excretion of unchanged sulfamethazine (18%) into urine and by formation of three metabolites subsequently excreted into urine. Sulfamethazine also was administered as a solution, a rapid-release bolus, and a sustained-release bolus. The change in the urinary metabolic pattern with different routes of administration suggested that first-pass metabolism was occurring during the absorption process. The absorption half-life was 6 hr. The absorption process for the two solid boluses kinetically appeared to include a dissolution step.

Keyphrases □ Sulfamethazine—absorption, metabolism, and excretion, various dosage forms compared, cattle □ Sulfonamides—sulfamethazine, absorption, metabolism, and excretion, various dosage forms compared, cattle □ Absorption—sulfamethazine, various dosage forms compared, cattle □ Metabolism—sulfamethazine, various dosage forms compared, cattle □ Excretion—sulfamethazine, various dosage forms compared, cattle □ Pharmacokinetics—sulfamethazine, various dosage forms compared, cattle □ Antibacterials—sulfamethazine, absorption, metabolism, and excretion, various dosage forms compared, cattle

Sulfamethazine is used extensively in veterinary medicine for the treatment of various infections in food-producing animals. Commercially available oral dosage forms for large animals include a solution, a bolus of the sodium salt, and a sustained-release bolus of the free acid. The comparative bioavailabilities and plasma concentration–time profiles of these dosage forms in large animals have not been reported.

The present study investigated the rate and extent of sulfamethazine absorption from three oral dosage forms compared with an intravenous solution of sulfamethazine sodium in 1-year-old cross-bred heifer feeder calves.

EXPERIMENTAL

Intravenous Administration—Three Hereford × Angus heifers, 1 year old, were weighed, fitted with urinary retention catheters[1] attached to 4-liter plastic collection bottles, and assigned to individual slot-floored metabolism cages 3 days prior to dosing. The weights of Animals 1, 2, and 3 were 235, 226, and 245 kg, respectively. Good quality grass hay and water were provided *ad libitum* during acclimatization and postdosing periods. A concentrate mixture, formulated from shelled corn and linseed meal and containing 12% protein, was limit fed to each animal during the study.

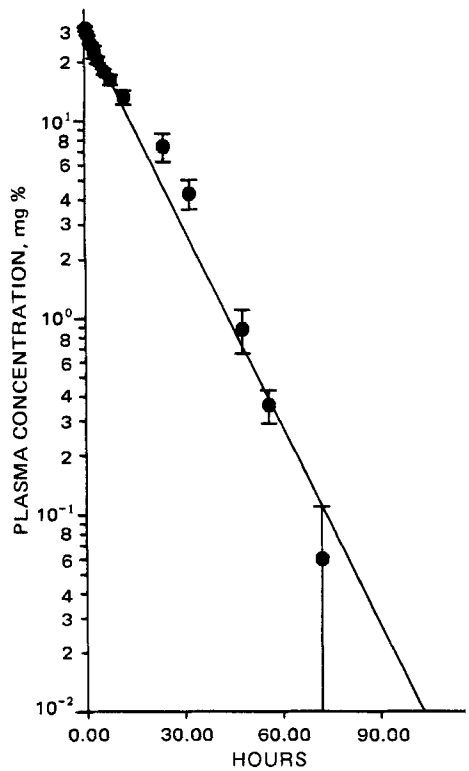

Figure 1—*Semilog plot of average plasma sulfamethazine concentration* (±SD) versus *time following intravenous administration of sulfamethazine sodium (107 mg/kg) to three calves. Points were experimentally observed, and the line was calculated by iterative least-squares fitting to a one-compartment model* ($t_{1/2}$ = *9 hr*, V_D = *0.35 liter/kg*).

A dose of 107 mg/kg (¾ gr/lb) of sulfamethazine as a 12.5% solution of sulfamethazine sodium[2] was rapidly injected *via* the right jugular vein in each animal. All blood specimens were collected from the left jugular vein by serial venipuncture using disposable plastic syringes prerinsed with a 1% solution of heparin sodium in normal saline.

Blood and urine specimens were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, and 72 hr following drug administration. The volume of urine collected over each interval was recorded, and a clean collection

[1] Bardex, 24 Fr, C. R. Bard Inc., Murray Hill, N.J.

[2] Prepared by diluting sulfamethazine sodium, 25% (American Cyanamid Co.), with an equal volume of sterile distilled water.