Intraperitoneal Fluid Infusion in Children with Gastroenteritis

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Summary: In a study of 91 babies with dehydration as a result of gastroenteritis the intraperitoneal route was found to be safe and effective in those with mild or moderate dehydration, but not in those who were severely dehydrated. The fluids found to be most effective in the intraperitoneal technique were normal saline with 28 mEq of potassium chloride per litre, or for hypertonically dehydrated babies half-strength Darrow's solution. This technique can be carried out by a nurse working single-handed if the baby is premedicated with promazine.

Introduction

Gastroenteritis is the commonest condition seen in the casualty department of the Lagos University Teaching Hospital, and probably in most paediatric casualty departments in the developing countries. During the 12 months April 1967 to March 1968 out of 10,135 patients seen in the emergency room 1,652 (16%) were treated for gastroenteritis and the mortality was 41 (10% of all deaths in the emergency room during the year). These babies died before they could be admitted to the wards.

The main form of treatment administered in the emergency room was rehydration by the intravenous route. Nevertheless, considerable skill and experience in this method of rehydration are indispensable if it is to be carried out safely and without adequate laboratory support, and clearly it is unsuitable for use in the remote areas of Nigeria and other developing countries. For this reason we decided to investigate the efficacy of the intraperitoneal route. This report is based on 105 intraperitoneal infusions undertaken to rehydrate children with gastroenteritis.

Materials and Methods

The children were first seen in the casualty department or in the general paediatric outpatient department of the Lagos University Teaching Hospital at Gbaja or Yaba. All had mild, moderate, or severe signs of dehydration according to the Medical Research Council classification (1952), quoted by Jelliffe (1961). The intraperitoneal infusions were performed by the method described by Carter (1953) after careful clinical examination and premedication with promazine (1 mg./lb. (0.45 mg./kg.) body weight). The average duration of the infusion was 9.8 minutes, and subsequently the wound was covered with sterile gauze and secured with Elastoplast or Nobecutane spray.

Twenty children were infused with 0.45 sodium chloride with potassium chloride (1 g. of KCl to 500 ml.); 21 with half-strength Darrow's solution; 21 with 0.9% sodium chloride with potassium chloride (1 g. of KCl to 500 ml.); 14 with full-strength Darrow's solution; and 15 with 0.45% sodium chloride in 2.5% dextrose with potassium chloride (1 g. of

KCl to 500 ml.). Each fluid was administered in a dose of 25 ml./lb. (11.4 ml./kg.) of body weight and was warmed to between 27 and 33° C. in a water-bath. Before and six hours after the infusion blood was withdrawn from each baby for the following estimations: haemoglobin level, packed cell volume (P.C.V.), serum electrolytes, and plasma osmolality. Plasma osmolality was determined with a Fiske osmometer. Six hours was chosen because it was thought to be long enough to judge the efficiency of treatment, and because it was about the end of a work-shift on the wards when nurses and doctors assessed the clinical state of children. The values of the variables measured before and after six hours were compared by the method of paired sampling, and the statistical significance of differences obtained was evaluated by Student's *t* test.

FIG. 1.—Effect of intraperitoneal infusion of 0.45% NaCl+KCl on P.C.V., plasma osmolality, and plasma Na⁺, K⁺, Cl⁻, and HCO₃⁻ (osmolality 195 mOsm/kg. H₂O). The points representing the values of each variable before and six hours after infusion are plotted around a line of identity. A shift towards the abscissa indicates an increase in the variable while a shift towards the ordinate indicates a decrease. The following are the mean changes of the variables: P.C.V., -1.63 ± 0.5 ($P > 0.1$); osmolality, $4.32 \text{ mOsm/kg.} \pm 1.05$ ($P < 0.01$); Na⁺, $0.05 \text{ mEq/l.} \pm 0.06$ ($P > 0.9$); K⁺, $0.81 \text{ mEq/l.} \pm 0.1$ ($P < 0.001$); Cl⁻, $3.23 \text{ mEq/l.} \pm 0.5$ ($P < 0.001$); HCO₃⁻, $1.53 \text{ mEq/l.} \pm 0.6$ ($P < 0.05$).

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Results

There was an equal distribution of sexes in the children studied. Their ages varied from 3 months to 4 years, 90 children being under 2 years of age. Of 91 children, 15 presented with mild, 51 with moderate, 3 with moderate-severe, and 22 with severe dehydration; the corresponding biochemical classification of the dehydration, as determined by electrolyte estimation and osmolality, was hypotonic in 78, hypertonic in 9, and isotonic in 4 (4.4%). The normal level of plasma osmolality was taken as 286 milliosmoles (mOsm) (Moore, 1959). In the Table the clinical state of the baby is compared with the results of biochemical estimations.

Clinical Assessment of Dehydration Compared with Tonicity of Plasma as Deduced from Serum Electrolytes and Osmolality

Clinical State	Hypertonic	Isotonic	Hypotonic	Total
Mild dehydration	1	1	13	15
Moderate dehydration ..	7	3	41	51
Moderate-severe dehydration ..	1	0	2	3
Severe dehydration	0	—	22	22
Total	9	4	78	91

FIG. 2.—Line of identity graphs showing effects of intraperitoneal infusion of half-strength Darrow's solution on P.C.V., plasma osmolality, Na^+ , K^+ , Cl^- , and HCO_3^- (osmolality 215 mOsm/kg. H_2O). For full explanation see legend to Fig. 1. The following are the mean changes of the variables: P.C.V., $-1.57\% \pm 0.36$ ($P < 0.001$); osmolality, 6.93 mOsm/kg. ± 1.02 ($P < 0.01$); Na^+ , 0.76 mEq/l. ± 1.1 ($P > 0.4$); K^+ , 0.39 mEq/l. ± 0.14 ($P < 0.01$); Cl^- , 2.34 mEq/l. ± 3.7 ($P > 0.5$); HCO_3^- , -1.09 mEq/l. ± 0.48 ($P > 0.4$).

During intraperitoneal infusion the reaction of 62 children was recorded. Forty-four passed a stool, 10 showed signs of discomfort despite their premedication, and two became dyspnoeic. One child was shocked, presumably because the water

was too hot, the temperature of the solution being 40°C ., which was the highest recorded in the series.

FIG. 3.—Line of identity graphs showing effects of intraperitoneal infusion of 0.9% $\text{NaCl} + \text{KCl}$ on P.C.V., plasma osmolality, Na^+ , K^+ , Cl^- , and HCO_3^- (osmolality 330 mOsm/kg. H_2O). For full explanation see legend to Fig. 1. The following are the mean changes of the variables: P.C.V., $0.1\% \pm 0.2$ ($P > 0.9$); osmolality, 14.7 mOsm/kg. ± 1.05 ($P < 0.001$); Na^+ , 3.85 mEq/l. ± 1.03 ($P < 0.001$); K^+ , 1.30 mEq/l. ± 1.07 ($P < 0.001$); Cl^- , 7.27 mEq/l. ± 1.0 ($P < 0.001$); HCO_3^- , 3.34 mEq/l. ± 2.1 ($P < 0.01$).

Of the total of 105 infusions 14 had to be abandoned at the end of the six-hour assessment period, as the children (all of whom were severely dehydrated) continued to deteriorate and needed to be resuscitated by the intravenous route. In most of the other children, however, vomiting and diarrhoea stopped within the first six hours. After this period it was possible to complete their rehydration orally with half-strength Darrow's solution. With this regimen 68 improved and were sent home within 24 hours of admission to hospital. There were 11 deaths, seven of these children being moderately severely or severely dehydrated. The remaining four children all died of bronchopneumonia and malnutrition—two had been adequately rehydrated, while in the other two the clinical state deteriorated six hours after infusion with half-strength Darrow's solution and they were put on intravenous fluids.

The biochemical changes produced after six hours by the treatment with various solutions are illustrated in Figs. 1–5.

With 0.45% sodium chloride + 1 g. of potassium chloride per 500 ml. the potassium and chloride ions were significantly absorbed and there was some haemodilution though the reduction of P.C.V. was not statistically significant.

With half-strength Darrow's solution a significant haemodilution occurred and potassium ions were absorbed. Sodium,

chloride, and bicarbonate ions were not significantly absorbed.

Infusions with 0.9% NaCl + 1 g. of KCl/500 ml. led to significant absorption of sodium, potassium, and chloride; serum bicarbonate was significantly lowered, and osmolality was significantly raised, but there was very little haemodilution.

FIG. 4.—Line of identity graphs showing effects of intraperitoneal infusion of full-strength Darrow's solution on P.C.V., plasma osmolality, Na^+ , K^+ , Cl^- , and HCO_3^- (osmolality 295 mOsm/kg. H_2O). For full explanation see legend to Fig. 1. The following are the mean changes of the variables: P.C.V., $1.0\% \pm 0.7$ ($P > 0.2$); osmolality, $8.45 \text{ mOsm} \pm 2.1$ ($P < 0.05$); Na^+ , $0.5 \text{ mEq/l.} \pm 3.2$ ($P > 0.9$); K^+ , $1.2 \text{ mEq/l.} \pm 0.2$ ($P < 0.001$); Cl^- , $-1.04 \text{ mEq/l.} \pm 1.3$ ($P > 0.4$); HCO_3^- , $3.1 \text{ mEq/l.} \pm 0.7$ ($P < 0.01$).

When full-strength Darrow's solution was infused, potassium ions were significantly absorbed and bicarbonate was significantly raised. The other ions were not significantly absorbed. Haemodilution was slight and osmolality was not significantly raised.

With 0.45% sodium chloride in 2.5% dextrose + KCl a significant absorption of potassium and chloride ions took place and plasma bicarbonate was significantly lowered. Sodium was not significantly absorbed, nor was there any significant haemodilution. Osmolality was significantly increased.

From specimens of stools collected in 60 cases pathogens were isolated in only 14 specimens (*Shigella flexneri* in nine cases, *Sh. schmitzii* in one case, and enteropathogenic *Escherichia coli* in four cases).

Discussion

Our experience has shown that intraperitoneal infusion of fluids is an effective method of treating babies dehydrated as a result of gastroenteritis. Moreover, it can be carried out by a

nurse working single-handed if the child is premedicated with promazine. The method needs very little supervision, as the required amount of fluid is allowed to run rapidly into the intraperitoneal space. Reactions to the infusion were generally mild, confirming the view of Blackfan and Maxcy (1918) and Carter (1953) on the safety of the method. Nevertheless, because of the large number of deaths and the necessity for intravenous therapy among the severely dehydrated babies, we believe that these babies should not be rehydrated by intraperitoneal infusion.

FIG. 5.—Line of identity graphs showing effects of intraperitoneal infusion of 0.45% NaCl in 2.5% dextrose + KCl on P.C.V., plasma osmolality, Na^+ , K^+ , Cl^- , and HCO_3^- (osmolality 333 mOsm/kg. H_2O). For full explanation see legend to Fig. 1. The following are the mean changes of the variables: P.C.V., $1.28\% \pm 0.5$ ($P > 0.05$); osmolality, $7.2 \text{ mOsm/kg.} \pm 1.4$ ($P < 0.01$); Na^+ , $0.2 \text{ mEq/l.} \pm 1.6$ ($P > 0.5$); K^+ , $1.21 \text{ mEq/l.} \pm 0.3$ ($P < 0.01$); Cl^- , $-6.1 \text{ mEq/l.} \pm 2.9$ ($P < 0.05$); HCO_3^- , $-1.88 \text{ mEq/l.} \pm 0.4$ ($P < 0.01$).

For complete replacement therapy a volume of 50 ml./kg. body weight is inadequate, particularly for moderately dehydrated babies, who need about 75 ml./kg. body weight to replace fluid loss. Hence it is our practice to start fluid therapy by mouth as soon as possible. From work in dogs with fluid containing radioiodinated serum albumin we found that fluid given by intraperitoneal infusion is absorbed most rapidly during the first two hours of infusion, and it should be possible to start oral fluids three hours after the infusion.

Early in the series a mildly dehydrated baby with hypertonic dehydration was given full-strength Darrow's solution intraperitoneally. Although water was absorbed as shown by a reduction of the packed cell volume, the plasma concentration of sodium and potassium and plasma osmolality rose alarmingly from 140 to 155 mEq/l., 4.2 to 6.4 mEq/l., and 292 to 294.5 mOsm respectively, as many of these children were oliguric.

It was therefore decided to use a solution containing less electrolyte, and half-strength Darrow's solution was found to be most suitable. It is important, therefore, for persons engaged in rehydrating babies in developing countries to be acquainted with the clinical presentation of children with hypertonic dehydration, and to avoid using hypertonic solutions such as normal saline or full-strength Darrow's solution intraperitoneally in these babies.

With all the solutions used there was significant absorption of potassium ion. This, we believe, was due to its high diffusion constant and concentration gradient. The peritoneal membrane

behaves in a non-selective manner and allows diffusion of electrolytes between it and the blood according to their concentration gradient.

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Clinical Evaluation of Adriamycin, a New Antitumour Antibiotic

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Summary: Adriamycin, a new antitumour antibiotic of the anthracycline group with a structural formula very similar to daunorubicin, has proved to have potent tumour-growth-inhibiting properties, and to be particularly effective in childhood malignancies. Though adriamycin produces a higher percentage of side-effects than daunorubicin—namely, stomatitis and alopecia—a lower dosage may be used for therapy.

Introduction

Adriamycin is a new antibiotic isolated in 1967 in the Farmitalia Research Laboratories from cultures of a mutant *Streptomyces peucetius* (*Streptomyces peucetius caesi*). The chemical structure of this compound (Arcamone, Cassinelli, Di Marco, and Gaetani, 1967) is very similar to that of daunomycin, from which it differs only in the substitution of a hydrogen atom with a hydroxyl group on the acetyl radical (Fig. 1). In acid media adriamycin is split into two components, a red pigmented water-insoluble aglycone (adriamycinone) and a water-soluble basis-reducing amino-sugar (daunosamine). Adriamycin belongs to the anthracycline group, as do daunomycin and rubidomycin (daunorubicin).

FIG. 1.—Structural formula of adriamycin.

The preliminary pharmacological studies were carried out by Di Marco, Gaetani, and Scarpinato (1969) at the National Cancer Institute of Milan. Adriamycin shows in some mouse and rat tumours a pronounced inhibitory effect on neoplastic proliferation followed by increased survival. Comparative studies showed that at equitoxic doses (2 and 2.5 mg. of adria-

mycin per kg. and 2.6 and 3.25 mg. of daunomycin per kg.) the survival time in C3H mice bearing lymphosarcoma was higher in animals given adriamycin, while the inhibiting dose (ID_{50}) was found to be 1.5 and 3.3 mg./kg. for adriamycin and daunomycin, respectively. The conclusion from these preliminary pharmacological studies is that adriamycin has a higher therapeutic index (1.25) than daunomycin (0.67). Furthermore, a lesser degree of leucopenia was observed in rabbits with adriamycin than with daunomycin, with the same dosage. A mild tachycardia without electrocardiographic abnormalities was recorded only in those rabbits controlled after two months (Bertazzoli, Chieli, Dell'Oro, Ferni, and Ricevuti, 1968).

The initial studies in man were started in the Clinical Chemotherapy Unit of the National Cancer Institute of Milan in September 1968. Up until May 1969 46 patients had been investigated. The pharmacological effects of the drug (dosage, therapeutic schedule, and toxicity) have been described in detail elsewhere (Bonadonna and Monfardini, 1969b).

From the present study adriamycin appears to be a drug which can produce a prompt effect in different types of neoplastic diseases with lower doses than those used with daunorubicin. The initial toxicity is mainly represented by extensive ulcers of the oral mucosa followed almost immediately by bone marrow depression and alopecia. In fewer cases leucopenia or loss of hair may be the first sign of toxicity. No appreciable changes in the liver and renal function tests have been observed, while no consistent cardiac abnormalities have been recorded.

The aim of the present study is to report the objective regressions obtained with adriamycin in leukaemia and in solid tumours of children and adults, as well as the side-effects found.

Materials and Methods

Thirteen children up to the age of 15 years (nine boys and four girls) and 33 adults with an average age of 47 years (26 men and seven women) have been adequately evaluated. Of the 46 patients reported in this study, 20 had previously received adriamycin and one or more courses of chemotherapy or radiotherapy or both.

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