ADVANCES IN CHOLERA-PATHOPHYSIOLOGY AND THERAPY

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Many advances in Cholera therapy have been made in the past few years. Before turning to therapy and management, however and in order to better understand therapy and management, I would like to review briefly our present knowledge and understanding of the physiology of Cholera.

Cholera is, of course, caused by an infection with the Vibrio Cholerae bacterium in the intestine producing massive diarrhoea, with this leading to dehydration and frequently to death. Long before the causative micro-organism was discovered, however, Dr. John Snow in 1854 ascribed the collapsed state of the patient to a loss of water, salt and alkali from the blood to the stool. He argued against the idea then generally accepted of a general toxemia caused by the infection. Many years later, precise balance studies by Dr. Phillips and his associates revealed that the Cholera stool contains about 140 meq of sodium, 15 meq of potassium, 100 meq of chloride and 45 meq of bicarbonate, with cnly minute quantities of protein. The massive rice water

diarrhoea which characterises cholera thus results in a loss of water and electrolytes from the body, in particular from the extracellular and intravascular space. Comparing the composition of the stool to that of serum, find that sodium and chloride are approximately the same but the potassium of the stool is three or more times that of serum, while the bicarbonate concentration in stool is twice that of normal serum; thus cholera results in a disproportionate loss of potassium and bicarbonate leading to a generalised deficiency of bicarbonate and a severe metabolic acidosis. Thus the cholera patient presents the symptoms of loss of fluid, that is a decreased blood pressure, perhaps to the point of not having a radial pulse, cyanosis in some patients, suppression of urine and, in some of the more severe patients, coma. The acidosis associated with this dehydration is seen as hyperventilation and also, interestingly enough as vomiting, I stress the fact that vomiting is associated with acidosis and dehydration, rather than with the infection itself, because we have found that the vomiting of cholera can be simply and rapidly eliminated by the correction of acidosis and dehydration with intravenous infusions of bicarbonate-containing solutions.

The excess potassium, because of the large intracellular stores of this ion, does not usually appear upon initial analysis of the blood as hypokalemia. In some cases, however, after correction of acidosis, we have seen serum potassium values as low I—1·2 meq per liter, with acompanying cardiac manifestations such as arrythmias and defects in conduction. Other manifestations of this loss of potassium are seen particularly in children. Many of our pediatric patients exhibit, on the second day of the disease, distension of the abdomen with very little bowel activity despite the continuation of diarrhoea. This gaseous abdominal

distension is frequently associated with a low potassium level in the blood, and is readily corrected by the oral or intravenous administration of potassium.

Thus, the clinical picture of cholera is found to be that produced by a loss of the non-protein elements of blood, that is, water, salt, potassium and bicarbonate, with a disproportionately high concentration in this loss of potassium and bicarbonate. The exact mechanism which causes this water and electrolyte loss in still not completely understood. Early studies in cholera, based on autopsies of patients who had died, showed that the intestinal mucosa had, in many cases, been destroyed. Thus, for many years, it was felt that the cholera vibrio organism invaded and destroyed the intestinal mucosa and that this destructive process was responsible for the diarrhoea of cholera. Biopsy studies of living cholera patients now have quite convincingly demonstrated that the intestinal mucosa is not destroyed by the vibrio. Both ordinary light microscopy and also eletron microscopy studies carried out in various parts of the world including our own laboratory in Dacca, have shown that the intestinal epithelial cells are quite healthy in appearance and that there are no demonstrable leaks in the intestinal capillary, endothelium or the intestinal epithelium itself, leaks which would permit larger molecular size elements such as protein molecules or red blood cells to escape into the intestinal lumen.

If the mucosa is essentially intact, what then causes the diarrhoea? Studies of the vibrio itself have now convincingly demonstrated that it releases to its surrounding medium a subtance, probably protein in nature, which acts upon the normal secretory and absorptive processes of the intestine and produces the diarrhoea. Reports of a few years ago suggested that the action of this toxin was

directly upon the "sodium pump", that active transport process which carries sodium against an electro-chemical and concentration gradient into the blood stream. Recent work has cost some of these conclusions into doubt but, although the sodium pump itself may be intact, sodium movement across the intestine is certainly abnormal. Studies at the Pakistan-SEATO Cholera Research Laboratory in Dacca, using radio isotope tracers in actively purging cholera patients, have shown that the pattern of abnormal sodium movement in the intestine can be characterised as both a decreased absorption of sodium from the intestine and also a some what increased secretion of sodium from the blood stream into the intestine. Thus, a net movement of sodium into the intestine takes place, carrying along with it the chloride ion and water. Various other exchanges take place subsequently, resulting in the addition of larger amounts of bicarbonate and potassium ions to this liquid in the intestinal lumen and it shortly appears, with the composition I mentioned before, the patient's rectum, seeking an exit.

With this brief review of our current understanding of the pathologic mechanisms responsible for the clinical picture of cholera, let us turn to a discussion of cholera therapy.

The treatment of cholera is fundamentally simple. The basic objectives, seen in the light of the causative mechanisms described above, are to replace the losses of water and electrolytes which have occurred before the patient seeks your medical attention and which continue to occur during the course of the illness. If this objective alone is reached, that is, intravenous fluid replacement therapy only is given, mortality from cholera can be decreased from 40 to 60% mortality rates in untreated patients to our success in Dacca of a mortality rate of less than

1%. In order to achieve success of this degree, however, the fluid replacement must be entirely in line with the pathophysiologic principles describes above, i. e. the bicarbonate and potassium lost in the stool, as well as the sodium chloride and water, or saline, must be replaced. It is our experience that treatment with saline alone will most likely result a mortality rate of from 7 to 15 or 20% depending upon the quantities of saline used. At the Pakistan-SEATO Cholera Research Laboratory a slightly hypotonic solution containing 5 grams of sodium choloride, 4 grams of sodium bicarbonate and 1 gram of potassium choloride, the resulting combination having almost precisely the exact composition of cholera stool, has proved to be an excellent single replacement solution for the treatment of adult cholera. Yet solutions of this sort are not readily available commercially in even the most cosmopolitan areas, and certainly not in many areas of Pakistan. Thus, some substitution utilising avilable resources must be used.

Phillips very carefully studied the result of administering various electrolyte solutions by mouth or by intestinal tube to actively purging cholera patient. He found that sodium and its accompanying water could not be absorbed if given by this route. He did find, however, that potassium and bicarbonate could be absorbed if given orally. Thus, if it is impossible to locate intravenous solutions or ampules of potassium or bicarbonante in order to aid them to the intravenous saline, one can administer potassium and bicarbonate by mouth to the cholera patient. Bananas and Dhab water are excellent sources of potassium and are easilly available in East Pakistan, while sodium bicarbonate can be found nearly every bazar, Physicians desiring the best possible care for their patients may thus add to intravenous saline therapy the administration of

oral potassium and bicarbonate and assure themselves of success with more than 99% of cases of their therapy.

As an alternative to the oral administration of bicarbonate, physcians both here and in Calcutta have found that acidosis can be avoided by the intravenous administration of isotonic sodium lactate, one-sixth molar lactate that is, with saline in the ratio of 2 liters of saline to each liter of lactate. The success of this regimen has been well demonstrated in adult patients. Pediatric patients, however, frequently requiring smaller amounts of fluid, may never receive that third liter designed to be lactate and may become severely acidotic as a result. Thus, although patients requiring amounts of intavenous fluid in excess of three liters, may be well handled by a therapeutic approach of this sort, the simultaneous administration of the bicarbonate and saline is definitely advantageous for smaller patients requiring less fluid and must be kept in mind by the physician caring for these patients.

How much fluid should be administered to the cholera patients ? Early workers in cholera emphasised the importance of limiting fluid administration because of the dangers of pulmonary edema developing from over administration. Using the balanced solution described above for our intravenous therapy, we and other workers have not found this to be a problem. Yet it was not until recently that studies demonstrated why pulmonary edema was not occurring in our patients. Scientisits from New York, working at our laboratory in Dacca, studied the pulmonary function, both gaseous and circulatory, in patients treated with saline only. They found first of all that these patients were uniformly severely acidotic with pH's in the range of 7·0 to 7·2 Secondly, they found that pulmonary circulatory dynamics were remarkable deranged resulting in a situation likely to end in pulmonary edema. This

abnormal circulatory condition in the lungs could be completely and rapidly abolished by the administration of bicarbonate bringing the patients out of acidosis and returning their pH to normal. We have found subsequently that overloading the patient with intravenous fluid is not a problem as long acidosis is net allowed to develop. The administration of saline, however, by allowing an initial acidosis to persist and, with the continuation of stool, to increase, may allow the patient to slip into pulmonary edema long before his plasma specific gravity or hematocrit, both measures of the degree of hydration, have returned to normal.

Providing then, that acidosis is kept mild and bicarbonate can be administered, either by the oral or intravenous route, how does one assess the amount of fluid required by the patient ? Phillips has utilised very effectively the plasma specific gravity as a simple measure of fluid requirement in the patient upon administration. He found that 0·4 milliliters of intravenous fluid per kilogram was required for each 0·001 elevation of the plasma specific gravity above normal. Administration of this amount of intravenous fluid would bring the plasma specific and hematocrit, as well as the pulse and blood pressure and other signs of dehydration, back to normal. Thus, if the dehydrated cholera patient is found, on admission, to have a plasma specific gravity of 1·035 and weighs 40 kilos, he would require 0·4 ml $\times$ 40 $\times$ 10 specific gravity units of intravenous fluid, or I,600 ml. to bring his plasma specific gravity back to normal. If copper sulphate solutions for measuring specific gravity are not available (I should stress here that these can be easily and extremely cheaply made by anyone having access to a balance), a more completely clinical method can be used to assess what replacement fluid is necessary. We have found that if the radial pulse is unobtainable, the patient has lost approximately 10% of his body weight in

diarrhoea, and will require that amount as replacement fluid. Thus, a woman weighing 30 kg. found to be pulseless as the result of diarrhoea will require 10% of 30 kg., i.e. 3 kg. or 3 liters of intravenous fluid to bring her state of hydration back to normal. The administration of less than this amount may be successful in keeping the patient alive and also will likely bring back the pulse. We have found, however, that only complete replacement of losses, frequently requiring large amounts of intravenous fluid, can result in the reduction of mortality rates to less than 1%, by avoiding complications such as kidney shutdown or cardiac arhythmias.

Following the initial dehydration, it becomes necessary to measure carefully the exact amount of stool excreted by the patient, and to replace this completely using either a balanced intravenous fluid or the combination of intravenous and oral administration mentioned above. Studies in our laboratory of the pattern of stooling by the cholera patient have shown that it is inadequate to measure only the frequency of stoool in order to assess the amount of diarrhoea present. It has been found that the cholera patient frequently will retain his stool for periods as long as two to three hours, giving the physician a false sense of security during this period. The patient then will pass in a large mass, one or $1\frac{1}{2}$ liters of diarrhoeal fluid at a time, fluid which has been accumulating in the intestine during that total three hour period. Thus, one patient may pass as much fluid in a single bowel movement as another patient who stools much more frequently, with only a small amount of stool being produced each time. Very simple equipment, such as buckets marked off in liters, facilitates this job of following the patient's output. Once the output is known, the physician then merely replaces it carefully.

Is there any place for antibiotics in the therapy of of cholera ? Studies at both the Pakistan-SEATO Cholera Research Laboratory and the Johns Hopkins Research Unit in Calcutta, as well as in the Philippines, have demonstrated that the administration of tetracycline, by eliminating the Vibrio cholerae from the intestine, will shorten the duration of diarrhoea and also decrease the total amount of stool produced by the patient during the course of his illness. In our hospital it was found that tetracycline could reduce the duration of diarrhoea from 4½ to only 2½ days and could reduce the total volume of stool produced in the hospital from 20 to 10 liters overall. Thus, by the administration of tetracycline, hospital beds can more rapidly released to new patients, and precious intravenous fluids can be conserved. From the preventive point of view, tetracycline administration also helps to reduced the likelihood of transmission of the infection from the convalescent patient to his neighbours after his return home.

In the ordinary, uncomplicated case, other drugs such as antiemetics, steroids, bowel relaxants and so forth, are not necessary and in fact may be harmful. We have found, however, that the pediatric patient with cholera may often present with coma secondary to hypoglycemia. Thus the immediate administration of intravenous glucose to a comatose pediatric patient may be effective and should be tried. Other complications of cholera, such as renal shutdown, aspiration pneumonia, convulsions, and so forth, are handled in the usual fashion in cholera patients.

This discussion of our conclusions regarding the ideal approach to cholera therapy based on current physiologic studies in the cholera patient brings us to a consideration of therapeutic studies still in progress in our Laboratory here in Dacca, and in other laboratories elsewhere,

Investigators in the past few years have demonstrated in vitro that glucose can increase the absorption of water and electrolytes in the cholera patient. This data was derived from balance studies and flux studies of the human cholera-affected small intestine, using radioactive tracers. During this past cholera season, it has been demonstrated in our Laboratory that a solution containing glucose, sodium, potassium, chloride and bicarbonate given orally along with tetracycline can reduce the intravenous fluid requirement in cholera by up to 80%. This is certainly a substantial reduction in the amount of intravenous fluid which a physician must administer and can lead to a great reduction in the cost of treatment to the patient. This form of oral glucose therapy in cholera might make successful treatment of cholera possible in isolated areas where intravenous solutions are scarce or not avilable. Studies have definitely shown that the method is effective and further studies are in progress to adapt the technique for large-scale clinical use by relatively untrained personnel.

A further development has been the testing of an intravenous solution containing acetate as a base precursor. As mentioned above, both bicarbonate and lactate can be used to correct the acidosis associated with cholera, but bicarbonate is difficult to sterilise and lactate is expensive. Acetate is inexpensive can be easily sterilised and is stable over a long period of time. We used acetate-containing solutions as a substitute for our usual balanced intravenous solution in both cholera and non-cholera diarrhoeal cases, and found it to be very effective in correcting acidosis and maintaining hydration. No complications of acetate administration were noted, and are able to recommend it as a substitute for lactate or bicarbonate solution in the therapy of cholera and other diarrhoeal diseases.

Recent work has also emphasised the need to consider pediatric cholera as somewhat different from the adult disease. Griffith, in the Philippines, and Rahaman at our Laboratory have found through precise balance studies that the stool of pediatric cholera cases is much higher in potassium and lower in sodium than the average adult Cholera stool. These studies thus emphasise even more the necessity for potassium administration either orally or intravenously in the pediatric case as well as a reduction in sodium and chloride concentrations in the intravenous fluids. Problems of hypertonicity can be avoided in the conscious pediatric patient by the administration of plain water by mouth but in the comatose patient, where the oral route is not available, the concentrations of electrolytes in the intravenous solution may require alteration.

Antibiotics other than tetracycline, have been and are being studied in our Laboratory in cholera cases. Furoxone, a nitrofurozan derivative, has been found to be as effective as tetracycline, and offers the advantage of a long shelf life. Ampicillin is currently under study in Dacca. *In vitro* studies show it to be effective against the Vibrio cholerae organism but clinical studies have not yet been completed. Early results suggest that a rather large dose may be required in order to have the same effect as a standard dose of tetracycline.

Although a discussion of prevention of disease is not perhaps appropriate in a Symposium on Diagnosis and Treatment, perhaps a brief mention of cholera prevention should be included here, in that if the disease could be prevented, all of these therapeutic measures would become unnecessary. Vaccine studies carried out at our field trial area in Matlab Bazar have demonstrated that cholera vaccine is effective in preventing the disease,

although not in 100% of those who receive it, and not for an extended period of time. These studies do show that use of the vaccine can be recommended at six-monthly intervals.

This brings me to the conclusion of this brief survey of current work in the field of cholera. All of these developments, of course, would not be possible without the knowledge gained from studies of the disease ; and it is anticipated that with further success in physiological, immunological and epidemiological studies, even better methods of prevention and treatment will evolve.

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