THE USE OF INTRAVENOUS UREA IN UPPER URINARY TRACT INFECTIONS

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Chronic pyelonephritis is a disorder which has been receiving a good deal of attention in recent years. The aetiology nevertheless is frequently obscure, the clinical manifestations are of infinite and deceptive variety and the results of antibiotic therapy are usually unsatisfactory. Diagnosis is too often finally established on the basis of irreversible changes radiologically demonstrated. It is well to realize that the conventional diagnosis of chronic cystitis, pyelitis, cysto-pyelitis, etc., may be associated with an inapparent renal infection which is progressive and ultimately fatal. It is a sobering observation that in a series of young women with acute pyelonephritis, at follow-up study 17 - 25 years later, Hanley[1] found 43% with serious renal changes.

The therapy of chronic pyelonephritis in the absence of exact knowledge defining those factors which enable bacteria to multiply so persistently in the kidney, is unrewarding at this time. During the period 1951 - 1956 for instance, the mortality from pyelonephritis in Danish women over 45 years of age increased two-fold.[2]

Wilbolz[3] recently reported that broad-spectrum antibiotics were completely useless in chronic pyelonephritis. Monzon *et al.*[4] in 1958 found that antibiotics had not solved the problem. The reasons for this may lie in interference with lymphatic drainage by inflammatory obliteration, or in lowered resistance offered by devascularized areas in the kidney, or in intrarenal stasis and obstruction. A combination of these factors may occur.

During 1961 Schlegel[5, 6] suggested a possible role for urea as a therapeutic agent in this connection, but provided little exact information as to mode and methods of administration, clinical indications or results. Urea therapy has been used in this department since July 1962 on cases unresponsive to antibiotic therapy, and the experiences gained on the first 23 cases will be reported here.

Certain properties of urea require elaboration to establish rationale of treatment.

Bactericidal Properties

These were first noted as long ago as 1906[7] and investigated sporadically during succeeding years.[8-12] Schlegel *et al.*[6] studied the effects of urea on *B. coli, Ps. aeruginosa, Proteus vulgaris, K. pneumoniae* and *S. albus*. A solution of 4% with 4-hour exposure was found to be bactericidal to all 5 organisms. Even a solution of 2% was strongly bacteriostatic to *K. pneumoniae, Proteus vulgaris,* and *E. coli*. A similar investigation was undertaken at the South African Institute for Medical Research in Johannesburg against *B. coli, B. proteus, Ps. pyocyaneus* and *Aerobacter aerogenes*. A 4% solution of urea was bactericidal to the first 3 organisms and bacteriostatic to the 4th. Within the limits of an *in vitro*-diffusion technique, urea appeared to enhance the effects of ampicillin, kanamycin sulphate and 'sulphatriad' against some of these organisms.

Property of Dissolving Dead Tissue

This property was first reported in 1900.[13] Tschiya *et al.*[14-16] in a series of articles reported that urea was a strong peptizing agent, with a marked solvent action for necrotic tissue, pus and debris. Holder and Nackay[17-20] have commented on this action, which occurs in varying degrees of acidity and alkalinity.

To emphasize the possible importance of this property the colloid plugs which occur in the tubules in chronic primary pyelonephritis should be remembered. The role of tubular obstruction, and the effects of urea on these plugs is speculative.

Diuretic Effect

Urea produces an excellent diuresis which may have a flushing effect on the kidney. Further, by reduction of intrarenal oedema improvement of drainage may be

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attained, and it is suggested that this is a significant factor in acute conditions.

ASPECTS OF ADMINISTRATION

The intravenous route was used in this series. Oral administration is possible in doses of up to about 120 G daily and produces a satisfactory urine concentration of urea although the diuresis is less than with IV administration. It is highly unpalatable, and appears less effective when given orally. The IV use of urea has been well documented following its introduction as a method for reducing intracerebral and intraocular pressure.[21] Experimentally, it produces an increase of renal oxygen consumption without an increase of renal blood flow, but appears safe if given slowly as an infusion.[22] Abnormal prothrombin times have been reported.[23] Thrombosis at the site of infusion has been reported in many series.[24-32] The effect on the serum electrolytes, in contradistinction to mannitol, appears to be benign. Mason and Raaf[23] report data indicating that a significant quantity of electrolytes is not lost with urea-induced diuresis. Indeed, in an unconscious neuro-surgical patient, care must be taken to avoid the production of an apparent hyperosmolarity.

To avoid the extensive superficial thrombophlebitis which occurs with administration into a vein of the arm, the drip was given into the vena cava, a polythene tube being introduced via the femoral vein by the Seldinger[33] technique. Two cases of deep-vein thrombosis occurred in the lower limb on the side of the puncture, and thereafter heparin was added to the drip, subsequent to which no further cases of thrombosis have occurred.

Dosage

The total IV fluid administered is 3,000 ml. daily for 5 days. This comprises one vaculitre of normal saline, plus 90 G of urea, plus 10,000 u. of heparin, and 2 vaculitres of 5% dextrose in water, each containing 45 G of urea and 5,000 u. of heparin. The preparation used throughout has been 'urevert' manufactured by Travenol laboratories. Oral fluid-intake should be reduced to a minimum. On this regime the urea concentration in the urine averages between 3 and 4% and diuresis amounts to around 5 - 7,000 ml. daily.

Side-effects

The blood urea rises, reaching in this series a maximum of 828 mg./100 ml. It is apparent that this will rise higher the poorer the renal function is, and that this factor will also limit urinary concentration of the urea. Headache is common, nausea fairly common. Two cases of deep-vein thrombosis occurred. Parotitis occurred in 1 patient not included in this series.

RESULTS

Results may be assessed on the basis of maintained sterilization of a previously infected urine, and/or improvement in the clinical course, in particular the disappearance or diminution of pyrexial flare-ups. Not all chronic pyelonephritics present maintained bacteriuria, and these are judged on a clinical basis in this series.

23 cases are available for assessment, comprising 15 cases of chronic primary pyelonephritis (1 medullary sponge kidney included), 4 cases of acute pyelonephritis and 4 cases of chronic pyelonephritis associated with unrelieved obstruction. All these cases had failed to respond satisfactorily to conventional and adequate antibiotic treatment.

Chronic Primary Pyelonephritis

These 15 cases comprise 14 females and 1 male. In 9 cases an organism or organisms were isolated from the urine at some time before the urea therapy. These organisms were *B. coli* in 4 cases, *B. proteus* in 2 cases, *Aer. aerogenes* in 1 case, *Aer. aerogenes* plus *Ps. pyocyaneus* in 1 case, and *Aer. aerogenes* plus *B. coli* in 1 case. Seven patients had infected urine when the course commenced. In 3 of these cases antibiotics were administered concurrently. At the conclusion of treatment the urine of all 7 patients was sterile. The remaining 8 patients had sterile urine when treatment commenced, and with one exception were given no concurrent antibiotics. In several instances a positive prednisolone provocative test became negative or the white-cell output in the urine declined sharply.

An effort was made in all these 15 patients to follow-up with long-term therapy by small doses of 'furadantin', 'madribon', 'gantrisin' or 'mandelamine'. One patient has been lost to follow-up. Six of the remaining 14 patients discontinued chemotherapy within 3 months of the urea treatment being completed. Eleven cases were followed for 11 - 17 months, and all had maintained sterile urine. Two cases each had one acute flare-up within this time. 3 cases were followed for 2 - 8 months. One of these had infected urine at 2 months, and subsequently underwent partial nephrectomy, and another—the medullary-sponge kidney—at 7 months had an acute flare-up with sterile urine. The third case still had sterile urine at 7 months.

These results may be compared with those of Pratt,[34] who found it impossible to abolish infection in 50 out of 84 cases. Mayo Clinic opinion[35] is that only 25% of chronic pyelonephritis can be controlled. A report by Turck[36] indicated initial sterilization by antibiotics in 62½% of cases, but check 6 weeks later showed maintained sterility in only 20%.

Chronic Pyelonephritis with Urinary Tract Obstruction

Four cases fall under this heading. In all cases the urine was infected and remained infected despite treatment by urea. This confirms the urological axiom that infection is uncontrollable where obstruction is present.

Acute Pyelonephritis

Four cases were treated. All had failed to respond to adequate antibiotic treatment. One case followed on cystoscopy and retrograde pyelography, and the remaining 3 occurred as complications of pyeloplasty. In all of this latter group, pelvic drainage by ureteric catheter or nephrostomy tube had been provided for several days before urea was exhibited. In 3 of the 4 cases the response was dramatic, with rapid subsidence of temperature and marked clinical improvement. Follow-up chemotherapy was provided with prompt urine sterilization when the drainage tubes were removed.

The fourth case developed septicaemia owing to *B. anitratum*. The source of this was uncertain, as it was not found in the urine, but *B. anitratum* is usually regarded as a hospital infection. This patient recovered completely.

CONCLUSION

In this series the use of urea was confined to the therapy of cases not responding to conventional and adequate doses of antibiotics. In both the cases of chronic primary pyelonephritis, and the cases of acute pyelonephritis, the response appeared to be satisfactory. In the latter cases in particular, it is felt that intrarenal oedema and tubular obstruction constitute a significant factor in resistance to antibiotic therapy.

SUMMARY

The inadequacy of conventional antibiotic administration in the therapy of pyelonephritis is underlined. The rationale of using urea and a method of administering it intravenously over a 5-day period is discussed. It is pointed out that careful supervision to avoid complications is necessary, and that the method, as applied to 23 recalcitrant cases, appears to be helpful.

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