Microcapsule Artificial Kidney and Medium Molecular Weight Clearance

T M S CHANG
McGill University, Montreal, Quebec, Canada

Since 1957 work in this and other laboratories on the care of semipermeable microcapsules as artificial cells has led to the demonstration of their clinical potential in the areas of enzyme replacement, detoxification and design of compact artificial kidneys (Chang, 1964, 1966, 1969, 1972; Chang et al, 1966, 1971, 1972; Sparks et al, 1971; Gardner et al, 1971; Andrade et al, 1971). The

Figure 1. The complete 300 grams ACAC microcapsule artificial kidney including tubing and temperature control heating tape. This is all the equipment and apparatus required for patients with external A-V cannulae. Scale in inches (2.54 cm)
to flow ratio of 300 g of ACAC microcapsules for medium molecular weight molecules is much higher. The clearance obtained with different types of artificial kidneys at flow rates of 200 ml/min is related to molecular weights in Figure 3. It is obvious from this diagram that, compared to other types of artificial kidneys, the microcapsule artificial kidney is much more efficient in the removal of medium molecular weight molecules.
Clinical effectiveness of the ACAC microcapsule artificial kidney

It has been demonstrated in earlier clinical trials (Chang et al, 1971, 1972) that two hours of haemoperfusion with the ACAC microcapsule artificial kidney resulted in the same symptomatic improvement in the patients as 6 hours of haemodialysis with the EX01 artificial kidneys. For example, a 71-year-old female was admitted with a diagnosis of terminal renal failure with nausea, vomiting, diarrhoea and malaise. In the first two months she received a total of 10.5 hours of haemodialysis on the EX01 and 9 haemoperfusions of 2 hours each with the 300 g ACAC microcapsule artificial kidney. On this regime, she became asymptomatic, ambulatory and able to carry out a useful life. After the two months' period, additional haemodialysis was given for the removal of urea, water and electrolytes, and she was maintained symptom free for another 6 months on an average weekly regime of 6 hours EX01 and 2 hours ACAC. There was no difference in her feeling of well-being when the 2 hours ACAC was replaced by 6 hours EX01 for the next 5 months. Another patient on standard treatment of 12 hours EX01 a week developed severe pruritus. The addition of 2 hours per week of ACAC microcapsule artificial kidney to her 12 hours per week EX01 haemodialysis has maintained her free from pruritus for one month. After this, the patient was
large surface to volume relationship and the ultrathin membranes of semipermeable microcapsules allow them to be used as a highly compact dialysis system. Thus, semipermeable microcapsules containing urease, ammonia adsorbents, ion exchange resins and activated charcoal have been demonstrated to be capable of removing uraemic metabolites and electrolytes. The albumin coated microencapsulated activated charcoal component (ACAC) does not release emboli and has no adverse effects on the formed elements of blood. Clinical trials indicate that two hours' haemoperfusion with 300 g ACAC (Figure 1) is as effective as six hours of standard haemodialysis with the EX01 artificial kidney, as far as the improvement of the patients' uraemic symptoms and general feeling of well-being is concerned. The search for uraemic toxins carried out extensively for many years by numerous investigators have resulted in impressive advances; however, the exact metabolites responsible for uraemic symptoms have not been firmly established (Merrill & Hampers, 1971).

The partial ACAC microcapsule artificial kidney is able to alleviate uraemic symptoms, even though it has not yet contained the components to remove urea, electrolytes or affect acid-base balance. Thus, in addition to its use in therapy, it may be used as an additional approach for the continuing search for metabolites responsible for uraemic symptoms.

METHODS AND PROCEDURES

Microcapsule artificial kidneys each containing 300 g of ACAC were prepared as described by the updated procedure (Chang, 1972). The clearances of creatinine and uric acid were obtained from published clinical data (Chang et al, 1971, 1972). The clearances of methyl orange (molecular weight 327), bacitracin (molecular weight 1430) and inulin (molecular weight 5200) were obtained in the present study.

RESULTS AND DISCUSSIONS

Clearance of medium molecular weight molecules

The clearance of different types of molecules are shown in Figure 2. It is interesting to note that the clearance to flow ratios for uric acid and creatinine remain constant up to a flow rate of 300 ml/min. This is unlike other types of artificial kidneys where the clearance to flow ratios decrease with increase in flow rate. The much higher efficiency of the microcapsule artificial kidney is due to the high surface to volume relationship and the ultrathin membrane (Table 1). With molecules of higher molecular weight (eg methyl orange) the clearance to flow ratio starts to decrease with increasing flow rate. With the much larger molecules like bacitracin and inulin, the clearance to flow ratios start to decrease even faster. Nevertheless, compared to the result obtained with the standard artificial kidneys, the clearance
put on a weekly regime of 6 hours EX01 and 2 hours ACAC per week for 3 months. During this period, the patient remained completely symptom free and with no pruritus. After this 4 months' period, when the patient was returned to the original weekly regime of 12 hours EX01 haemodialysis for one month, pruritus reappeared. The addition of weekly 2 hours' ACAC haemoperfusion again resulted in the disappearance of the pruritus after two weeks of treatment.

Another patient on 12 hours per week EX01 when changed to 6 hours EX01 and 2 hours ACAC remained symptom free. These and other patients feel that their general feeling of well-being is as good if not better when one of the two 6 hours weekly EX01 is replaced by 2 hours of ACAC. In addition, the much shorter duration of haemoperfusion required is such that patients feel much less fatigued after the treatment. Thus, after a standard 6 hours EX01 haemodialysis, the patients usually feel tired and have to rest at home in the evening; on the other hand, with the 2 hours ACAC haemoperfusion, the patients come in after lunch to receive 2 hours of haemoperfusion and then return home ready to carry out their usual activities.

![Figure 4](image_url)

**Figure 4.** Total clearance for two hours or six hours perfusion on the ACAC microcapsule artificial kidneys (200 ml/min) compared to the total clearance obtained with six hours haemodialysis on the EX01 artificial kidney
ANALYSIS OF CHARACTERISTICS OF METABOLITES RESPONSIBLE FOR URAEMIC SYMPTOMS

Since the 2 hours' haemoperfusion with the ACAC appears to be comparable to 6 hours of haemodialysis with the EX01, as far as the alleviation of uraemic symptoms and general feeling of well-being is concerned, the total clearance to molecular weight curves for the two systems are compared in Figure 4. Here the total clearance obtained with 2 hours on the ACAC microcapsule artificial kidney is compared to the total clearance obtained with 6 hours of EX01 haemodialysis. This figure shows that as far as molecules with molecular weights around 200 are concerned, a greater total amount of molecules were removed after 6 hours perfusion with the EX01 than after the much shorter 2 hours with the ACAC microcapsule artificial kidney. The curves for 2 hours ACAC and 6 hours EX01 cross at a molecular weight of approximately 800. Above a molecular weight of 800 a greater total amount of molecules was removed after 2 hours with the ACAC microcapsule artificial kidney than after 6 hours with the EX01. If the amount of removal of the metabolites causing symptoms can be directly related to the relief of uraemic symptoms, then 2 hours with the ACAC should remove approximately the same amount of these metabolites as 6 hours with the EX01. If this is true, then the present result would suggest that metabolites responsible for uraemic symptoms may have a molecular weight of about 800. With further increase in molecular weight beyond 800, the comparative total removal becomes increasingly greater for the 2 hours ACAC; on the other hand, with molecular weight of greater than 1200, the total clearance obtained would not be sufficient to account for the improvement observed. Thus, the metabolites responsible for the uraemic symptoms of nausea, vomiting, diarrhoea, pruritus and malaise are most likely to have molecular weights in the range of 600 to 1200.

It is interesting to note that using uraemic neuropathy as a guide, Babb et al (1972) have demonstrated a relationship between the efficiency of plate, coil and hollow fibre artificial kidneys and their ability to remove molecules in the 300 to 1000 molecular weight range.

ACKNOWLEDGMENTS

This study was supported by grants MRC-SP-2 and MRC-MA-2100 from the Medical Research Council of Canada.

The technical assistance of Miss E Tarro and Miss M Michelsen in the analysis of bacitracin, methyl orange and inulin and the preparation of the illustrations by Mr K Holeczek is appreciated.
REFERENCES

Chang, T. M. S. (1964) Science, 146, 524

574