Middle Molecule Clearance in Current Dialysers

B von HARTITZSCH, N A HOENICH, R J PETERSON, T J BUSELMEIER, D N S KERR, C M KJELLSTRAND

University of Minnesota Hospital and North Star Research and Development Institute, Minneapolis, USA and University of Newcastle upon Tyne and Royal Victoria Infirmary, Newcastle upon Tyne, UK

The clinical problems of neuropathy, pericarditis, and other complications developing in some dialysis patients led to the proposal of the square meter hour hypothesis (Babb et al, 1971) and its more recent modification, the middle molecule hypothesis (Babb et al, 1972a). Both theories suggest that inadequate removal of the middle molecules (MW 300-2,000) might be the cause of these complications. Although no middle molecules have been isolated or proven to be the cause of these complications, the theories have a profound influence on dialysis protocols with numerous clinical studies resulting in a confusing and conflicting array of results (Kjellstrand et al, 1972). Failure to consider the effect of residual renal failure on middle molecule concentration (Kjellstrand et al, 1972; Babb et al, 1972b) and inaccurate determinations of the clearance of middle molecules for various dialysers are possible explanations for this confusion. Another possibility is that factors other than middle molecules are responsible for many of the ill effects in dialysed patients.

This paper presents middle molecule clearances for most currently available haemodialysers.

METHOD

Sodium diatrozoate (hypeaque MW 630) and cyanocobalamine (vitamin B$_{12}$ MW 1,355) were chosen as solutes representative of the middle molecules (von Hartitzsch et al, 1972). $^{125}$I-Na diatrozoate and $^{58}$Co cyanocobalamine were diluted in three litres of physiological saline and perfused through the blood compartment of the various dialysers with a 'blood flow' of 200 ml/min. Dialysis fluid was produced by a proportioning unit at 500 ml/min at 37°C. Concentrations of the isotope in samples collected at the arterial and venous ends of the dialyser were counted in an autogamma counter to an error of less than 1%. In a few studied crystalline B$_{12}$ was diluted to a concentration of 0.5mg/100 ml and measured spectrophotometrically on a Beckman DU
spectrophotometer at 358 nanometers. Three sets of samples 5 minutes apart were taken from each dialyser after an initial stabilisation period of 15 minutes. In vitro clearances corrected for ultrafiltration were calculated from the formula: Clearance = Bloodflow (arterial concentration - venous concentration) / arterial concentration + ultrafiltration rate (C=Q_{B} \frac{a-Y}{a} + u). Isotope stability was monitored constantly by using a control dialyser, the MPS (Meltec) 1 m² Kiil twice a day. This is essential as B_{12} and hypaque become altered by persistent exposure to light and tap water, resulting in considerable decreases in clearance compared to those observed when the isotopes are dissolved in physiological saline and kept in the dark.

RESULTS

The in vitro measured middle molecule clearances are shown in Table I along with small molecule (urea and creatinine) clearances obtained in vivo (von Hartitzsch et al, 1973a). The results for other dialysers calculated from those measured results are shown in Table II.

Table I. Comparative Clearances of Small and Middle Size Molecules

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>In Vivo</th>
<th>In Vitro*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urea MW 60</td>
<td>Creatinine MW 113</td>
</tr>
<tr>
<td>Multipoint Pyramid Support Kiil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meltec 1 m² 11μ Cup.</td>
<td>140</td>
<td>113</td>
</tr>
<tr>
<td>Meltec 1 m² 18μ Cup.</td>
<td>130</td>
<td>104</td>
</tr>
<tr>
<td>Meltec 0.6 m² 11μ Cup.</td>
<td>116</td>
<td>90</td>
</tr>
<tr>
<td>Standard Kiil 1 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson Marlow 11μ Cup.</td>
<td>96</td>
<td>73</td>
</tr>
<tr>
<td>Gambro Lundia 18μ Cup.</td>
<td>104</td>
<td>87</td>
</tr>
<tr>
<td>Ultraflo 100 Coil 18μ Cup.</td>
<td>120</td>
<td>99</td>
</tr>
<tr>
<td>Cordis Dow Hollow Fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3 1 m² 30μ</td>
<td>126</td>
<td>97</td>
</tr>
<tr>
<td>Model 4 1.3 m² 30μ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Middle molecule clearances corrected for minimal ultrafiltration produced in obtaining blood flow 200 ml/min and dialysate flow 500 ml/min ± standard deviation. Temperature 37°C. Calculated clearances in parenthesis.
<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Membrane</th>
<th>Measured In Vivo</th>
<th>Predicted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Urea MW 60</td>
<td>Creatinine MW 113</td>
</tr>
<tr>
<td>Rhône Poulenc ID 8 layer</td>
<td>12µ Cup.</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>Drake Willock DB33 Disposable multipoint 0.68m²</td>
<td>11µ Cup.</td>
<td>105</td>
<td>85</td>
</tr>
<tr>
<td>Dasco SP 400 Disposable multipoint</td>
<td>13.5µ Cup.</td>
<td>108</td>
<td>88</td>
</tr>
<tr>
<td>Nephravon Coil</td>
<td>18µ Cup.</td>
<td>119</td>
<td>102</td>
</tr>
<tr>
<td>Ultraflo 2 coil cartridge</td>
<td>18µ Cup.</td>
<td>113</td>
<td>91</td>
</tr>
<tr>
<td>EX-03 coil cartridge</td>
<td>18µ Cup.</td>
<td>114</td>
<td>92</td>
</tr>
</tbody>
</table>

*Blood flow 200ml/min. Dialysate flow 500ml/min. Temperature 37°C.
DISCUSSION
The results of the MPS Kill show that an increase in membrane thickness from 11\( \mu \) to 18\( \mu \) results in only a 7-8% decrease in clearance of small molecules, but a 31-36% reduction in clearance for middle molecules MW630 - 1,355. Middle molecule clearances relative to small molecule clearance are further reduced when membrane thickness is increased even more as is shown in the results of the Cordis Dow Hollow Fiber kidney with a 30\( \mu \) membrane. Effective surface area, that is the percentage of actual membrane area not masked by membrane support and in contact with flowing blood and dialysis fluid, is the other major determinant of dialyser clearance. Inherent problems in dialyser design that produce unequal flow between compartments, and membrane masking by blood clots will reduce the effective surface area, decreasing performance in a manner analogous to a ventilation perfusion defect in the human lung. The identical performance of the larger 1.3 square meter surface area Cordis Dow Model 4 to the 1m\(^2\) Cordis Dow Model 3 is probably due to maldistribution at the blood and dialysis flows used by us, resulting in an effective surface area of approximately 1m\(^2\) for both dialysers.

As small molecule removal is mainly flow dependent, differences in small molecule clearance between dialysers of similar surface area have been assumed to be due to different flow patterns. However, theoretical concepts indicate that a velocity increase considerably in excess of the clinical ranges would be required to alter the laminar flow characteristics to turbulent flow with improved mass transfer rate (Keller, 1973). In the clinical setting we found that similar incremental increases in performance occur in most currently available dialysers as blood and dialysis flow are similarly varied (von Hartitzsch et al., 1973a). Thus, comparative dialyser clearances for both small and middle molecules are mainly determined by membrane thickness and effective surface area. Therefore, when dialysers with similar membranes are compared it is not surprising that the measured middle molecule clearances are in the same ratio as the urea and creatinine clearances. This enables one to reasonably approximate middle molecule clearances for other dialysers using the following formula:

\[
\frac{\text{Clearance Creatinine}_A}{\text{Clearance Creatinine}_B} = \frac{\text{Clearance Middle Molecule}_A}{\text{Clearance Middle Molecule}_B} \times \frac{\text{Effective Surface Area}_A}{\text{Effective Surface Area}_B}
\]

It is obvious that this formula can be used only when both dialysers to be compared have exactly the same membrane. The accuracy of this assumption is shown in Table I where the in vivo and in vitro clearances of middle molecules calculated according to this formula are given. The numbers in parenthesis are based on in vivo BUN and creatinine clearances and compare with those actually measured in vitro.

The study of the middle molecule clearances (Tables I and II) show that
most present-day dialysers have potentially similar middle molecule clearance. The exceptions are the very efficient multiple point support Kiil and the relatively inefficient Cordis Dow dialysers. Except for these two dialysers, it is immaterial which dialysers one chooses. If middle molecule clearance is unimportant, the Cordis Dow will not be inferior to the other dialysers. If on the other hand removal of middle molecules is important, the dialysers of choice would be the Multiple Point Support Kiil, Meltec*, using $1_{\mu}$ membranes.

The importance of middle molecules as causes of dialysis complications is unclear. Originally, neuropathy was said to be caused by middle molecules (Babb et al, 1971). However, in a recent study of 30 anephric patients dialysed for more than 150 days, Kjellstrand et al (1973) found that both the severity of uraemia at the onset of dialysis and the degree of uncooperativeness (degree of hypertension, hyperkalaemia, and fluid accumulation prior to each dialysis) correlated much better with the presence of neuropathy than theoretically calculated middle molecule levels.

Only in the high risk patients who had extreme uraemia at the start of dialysis and who were unable to cooperate did it seem important to remove middle molecules. Rapid ultrafiltration (Meyrier et al, 1972), rapid fluctuations in levels of uraemic toxins (Tyler, 1968), and hypertension (Povtizer et al, 1969) have been associated with neuropathy in dialysis patients. These are the factors to which the uncooperative patient is exposed. Drastic reductions in middle molecule clearance in dialysed patients have not been accompanied by neuropathy (Berman et al, 1973; Cambi et al, 1973), but a greater need for dietary and fluid restriction was required to cope with the less frequent dialysis.

Pericarditis developing in dialysis patients has been attributed to underdialysis and linked with middle molecule clearance. However, recent studies (Buselemeier et al, 1973) indicate a specific febrile syndrome frequently unresponsive to intensive dialysis.

Before relating any new parameters of adequacy of dialysis such as haemolysis (von Hartitzsch et al, 1973b), anaemia etc to middle molecule clearance it would be well to consider that better control of fluctuation in fluid, acidosis, phosphate, and electrolytes that come with greater cooperation and more frequent dialysis could eliminate more of these problems.

CONCLUSION

Comparative middle molecule as well as small molecule clearances are largely dependent on effective surface area and membrane characteristics.

---

*Meltec Ltd (Milton Roy), Bourne End, Buckinghamshire, England
Middle molecule clearance can be calculated for most dialysers, based on
known small molecule clearances.

Different combinations of membrane permeability and effective surface
area have fortuitously resulted in similar middle molecule clearances for
most commonly used dialysers. The exceptions are the Multiple Point Support
D₄ Kiil and the less efficient Cordis Dow Hollow Fiber Kidney. We believe
no dialyser should be claimed to be superior because of improved middle
molecule clearance. Other factors seem to be more important in preventing
or causing neuropathy in dialysed patients. Severe uraemia at the initiation
of dialysis and uncooperativeness on the part of the patient are particularly
detrimental to nervous function.

REFERENCES

Babb, A. L., Popovich, R. P., Christopher, T. G. and Scribner, B. H.
(1971) Transactions. American Society for Artificial Internal Organs,
17, 81

Transactions. American Society for Artificial Internal Organs, 18, 98

and Scribner, B. H. (1972b) Proceedings Dialysis and Transplant Forum,
2, 142

American Society for Artificial Internal Organs, 2, 5

Buselmeier, T. J., Simmons, R. L., Najarian, J. S., von Hartitzsch, B.,
Dietzman, R. H. and Kjellstrand, C. M. (1973) Proceedings of the
European Dialysis and Transplant Association (this volume)

Cambi, V., Arisi, L., Buzio, C., Rossi, E., Savazzi, G. and Migone, L.
(1973) Abstracts. American Society for Artificial Internal Organs, 2, 10

American Society for Artificial Internal Organs, Page 57

Kjellstrand, C. M., Evans, R. L., Peterson, R. J., Rust, L. W.,
Shideman, J. R., Buselmeier, T. J. and Rozelle, L. T. (1972) Proceed-
ings of the Dialysis and Transplant Forum, 2, 127

Kjellstrand, C. M., Peterson, R. J., Evans, R. L., Shideman, J. R., von
Hartitzsch, B. and Buselmeier, T. J. (1973) Transactions. American
Society for Artificial Internal Organs, 19 (in press)

2, 252

Popovtzer, M. M., Rosenbaum, B. J., Gordon, A. and Maxwell, M. H.

Tyler, H. R. (1968) American Journal of Medicine, 44, 734


von Hartitzsch, B., Hoenich, N. A., Samson, P., Erickson, J., Ashcroft,

von Hartitzsch, B., Carr, D., Kjellstrand, C. M. and Kerr, D. N. S. (1973b)
Transactions. American Society for Artificial Internal Organs, 19 (in press)