Statement from the Regional HTA Centre of the Western Region in Sweden

Effect of atrial natriuretic peptide, ANP, on the need for dialysis, when used as treatment or prevention of acute renal failure in intensive care.

The Regional Health Technology Assessment Centre (HTA-centrum) of the Western Region in Sweden (Region Västra Götaland, VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, economical and ethical aspects of the particular health technology that has been assessed in the report.

Per Nellgård, Head of the Department of Cardiothoracic Anesthesia and Intensive Care and Sven-Erik Ricksten, professor and senior consultant from the same department requested the present HTA.

A working group, appointed by the Head of the Department, including the above mentioned persons and Johan Malmgren M.D., at the same department, produced the HTA report.
The participants from the HTA centre were Annika Strandell, MD, PhD, Christina Bergh, professor, and Ulla Wikberg and Eva-Lotte Daxberg, information specialists.
Ulla Molander, MD, PhD and Åsa Axelsson, PhD have critically appraised the report.

The project lasted during the period: 2009-03-25—2009-06-10

Question at issue:
Can treatment and prevention of acute renal failure with ANP reduce the need for dialysis in intensive care patients?

PICO

P = Adult patients with, or at risk for, acute ischemic renal failure after major surgery, organ transplantation or in association with cardiac failure.
I = Natriuretic peptides (ANP, anaritide, nesiritide, urodilatin)
C = Conventional treatment or placebo
O = Primary outcome:
Need for dialysis (dichotomous, YES or NO)
Secondary outcomes:
Mortality
Renal function measured as “GFR”, "creatinine clearance" and/or "peak creatinine"
Complications
Length of stay in intensive care unit(ICU)/hospital

Summary of the health technology assessment:

Method and patient category:
In association with major surgery or organ transplantation acute renal failure which requires dialysis occurs frequently. It is associated with a high mortality despite intensive care. Patients with acute renal functional impairment are treated with diuretics, inotropic drugs and when needed dialysis. ANP is an endogenous peptide, which dilates the renal vasculature and may thereby improve renal function in the early phase of functional impairment. Treatment or prevention of acute renal failure with ANP may have the potential to reduce the need for dialysis, and subsequently also the length of stay in the intensive care unit. The use of ANP is presently not an established treatment for renal failure, but has been used in major paediatric surgery.

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Level of evidence:
The literature search resulted in inclusion of two systematic reviews and nine randomised studies. All original articles have been given a quality rating (high, medium or low), and the effect of ANP has been evaluated in four various patient categories (see below). The level of evidence has been rated according to the GRADE system in a four-step scale (high, medium, low or very low), and has been graded only for the primary outcome, i.e. need for dialysis.
The effect of ANP in the patient categories are presented as prevention and/or treatment depending on whether ANP therapy was initiated before the development of or after established acute renal failure.

Effect of ANP on the outcome Need for dialysis

- General population of ICU patients

Prevention of acute renal failure
One systematic review included 11 studies (818 patients). It showed a reduced need for dialysis, approximately by 50%, but the size of the effect is uncertain. Low level of evidence (++).

Treatment of acute renal failure with low dose ANP
The same systematic review as above included six studies (282 patients). It showed a reduced need for dialysis, approximately by 50%. Low level of evidence (++).

Treatment of acute renal failure with high dose ANP
The same systematic review as above included three studies (185 patients). It showed no effect on the need for dialysis. Low level of evidence (++).

- Postoperative patients

Treatment / prevention of acute renal failure
The same systematic review as above included 14 studies (817 patients). It showed a reduced need for dialysis, approximately by 50%. Low level of evidence (++).

- Cardio-vascular surgery

Treatment /prevention (low dose) of acute renal failure
A second systematic review included 11 studies (596 patients). It showed a reduction of more than 60% of the need for dialysis. Medium level of evidence (+++).

- Organ transplantation

Treatment /prevention (low dose) of acute renal failure
Five studies (180 patients) were included in a new meta-analysis. It showed a reduction by approximately 50% of the need for dialysis. After the exclusion of two studies of low scientific quality, the treatment effect was no longer statistically significant. The conclusion that ANP reduces the need for dialysis has a low level of evidence (++).

Effect of ANP on the outcome Mortality
No statistically significant reduction of mortality has been observed in any of the individual studies or in the meta-analyses of treatment/prevention of ICU-patients in general, postoperatively or after cardio-vascular surgery.

Effect of ANP on the outcome Renal function (measured as GFR, peak creatinine or creatinine clearance)
An improved renal function was demonstrated in the following patient categories:
- prevention in ICU patients.
- treatment/prevention (low dose) after cardio-vascular surgery (according to systematic reviews).
- treatment/prevention (low dose) after organ transplantation (one study of medium quality).
With regard to treatment of acute renal failure in patient with cardiac failure, two of four studies demonstrated an improved renal function whereas two did not.

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Effect of ANP on the outcome Length of stay at ICU/ hospital.
The stay at ICU was shortened in the following patient categories:
- treatment/prevention (low dose) of ICU patients in general.
- treatment/prevention (low dose) after cardio-vascular surgery.

All effects in the above stated outcomes are statistically significant.

Complications:
Hypotension developed frequently, particularly during treatment with high dose ANP. According to the systematic reviews, both hypotension and arrhythmias were significantly more common after treatment with high dose ANP compared with placebo-treated controls. No other side effects where reported.

Ethical aspects:
Is it ethical not to use ANP to reduce the need for dialysis in populations in which patient benefit has been demonstrated?

Economical aspects
The costs for treatment with ANP is high, approximately 5.500 SEK/day. However, the calculated reduction in dialysis (14.000 SEK/d) and the shortened length of stay at the ICU (25 000 SEK/d) can compensate for the cost of the drug. A calculation indicates a net cost reduction of 30-45% (9-12 million SEK/year).

Concluding remarks

Acute renal failure following major surgery, including organ transplantation, often requires expensive dialysis care. Treatment and prevention with the use of ANP may reduce the need for dialysis by half in specific patient populations. The largest effect has been observed in patients with acute renal failure after major cardio-vascular surgery where the need for dialysis decreased to one third.
The effect of ANP is clearly present in low dose treatment, but missing at high dose. Complications, mainly hypotension, are few and related to the dose. Future studies are particularly needed in patients following organ transplantation.

On behalf of HTA-centrum Göteborg, Sweden, 2009-06-10

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