Toxic serum gentamicin levels after the use of gentamicin-loaded sponges in infected total hip arthroplasty

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Background **At our clinic, total hip arthroplasties with an acute postoperative infection are treated with surgical debridement and application of several gentamicin-loaded sponges, each with an equivalent of 130 mg gentamicin. We studied the possible systemic effect of this local application of gentamicin.**

Patients and methods **All 12 patients treated during 1997–2001 were included. 4–6 sponges were used in each case. We measured the serum gentamicin levels daily, from the first postoperative day until gentamicin was no longer measurable. The creatinine levels were monitored daily and the creatinine clearance was calculated according the Cockcroft-Gault formula.**

Results **In 7 of the 12 patients, we found toxic serum levels of gentamicin (range 2–13 mg/L). In 3 cases there was a significant drop in renal clearance, which persisted. In 3 other cases there was a temporary decrease in renal clearance.**

Interpretation **We found toxic serum levels after local administration of gentamicin. We even found a persistent decrease in renal clearance in some patients. Because of the alarming results, we have reduced the number of sponges used for this purpose.**

In early postoperative deep hip prosthesis infections, debridement, suction-irrigation drainage and systemic high-dose antibiotics may be effective if the treatment is initiated within 24–36 h of the onset of signs of infection (Buchholz et al. 1981, Anttipoika et al. 1990, Gambhir et al. 2000, Haddad and Ridgway 2001). In other cases, removal of the prosthesis is recommended. In our clinic, total hip arthroplasties with an acute postoperative infection are treated with surgical debridement, irrigation, retention of the prosthesis and application of several gentamicin-loaded sponges. Systemic administration of antibiotics is started and, depending on the results of the cultures, adjusted to the sensitivity of the bacteria.

Gentamicin is known to have systemic adverse effects such as ototoxicity and nephrotoxicity. It is less well-known that there can be worsening of neuromuscular disorders e.g. myasthenia gravis, resulting in muscular weakness and respiratory depression. Aminoglycosides have a narrow therapeutic index. After intravenous administration, bioavailability is 100%, and peak serum concentrations occur at the end of the infusion. After intramuscular administration, bioavailability is also usually 100%, and peak serum concentrations occur after 30–90 min. Gentamicin administered intravenously has a half-life of 2 (0.5–3) h in adults. The therapeutic serum level has a range of 4–10 microgram/mL. 30–100% of the gentamicin is disposed of within 24 hours by renal excretion in unchanged form. The subject of this study was to assess whether the local application of gentamicin (Garacol, Duracol, Gentacol) has a significant systemic effect.

Patients and methods

Between 1997 and 2001, all 12 patients (8

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Table 1. 12 patients treated with gentamicin-loaded sponges 1997–2001

	Men (4)	Women (8)
Age, mean (SD)	68 (12)	72 (7)
Weight (kg), mean (SD)	91 (21)	85 (12)
ASA [a] classification, n		
1	0	0
2	2	6
3	2	2
4	0	0

[a] ASA, American Society of Anesthesiologists physical status classification (Owens et al. 1978)

Table 2. Observations

Patients	Total follow-up (month)	Maximum serum levels of gentamicin (mg/L)	Creatinine clearance decrease at final follow-up (mL/min)
1	42	0.3	10
2	6	1.4	31
3	2	4.5	33
4	10	5.7	31
5	27	0.3	–20
6	12	6.7	–4
7	16	6.4	–2
8	36	6.9	20
9	2	3.2	10
10	13	13.2	5
11	13	1.0	8
12	22	1.4	9

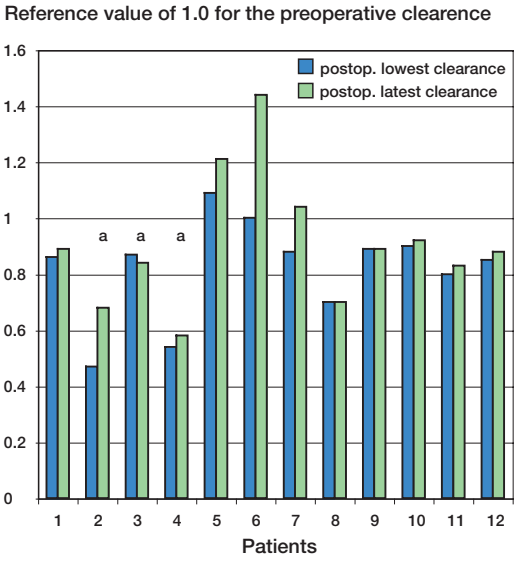

Figure. Changes in postoperative creatinine clearance relative to preoperative clearance in 12 patients treated with gentamicin-loaded sponges 1997–2001. The y-axis shows a reference value of 1.0 for the preoperative clearance in each individual case. [a] Indicates a patient with clearance decrease of more than 2 SD.

women) with an acutely infected primary total hip arthroplasty (mean age 71 (54–83) years) were included prospectively (Table 1). The prostheses could all be retained. The patients were followed systematically, and the reasons for surgery were arthrosis (8) and aseptic loosening (4).

A surgical debridement was performed, and samples in the form of swabs and tissue were taken for cultures. Pulsatory lavage was used before several gentamicin-containing sponges were introduced into the wound just before closing. The preparation used was Garacol 10 × 10 × 0.5 cm, with an equivalent of 130 mg gentamicin. It contains a bovine collagen as a carrier, which is fully biodegradable. 4 or 5 sponges (and in 1 patient, 6) were applied. The manufacturer (Schering-Plough, Maarssen, the Netherlands) advises a maximum of 5 sponges in the case of osseous infections. Postoperative intravenous antibiotics were started, but no gentamicin was given. Gentamicin serum levels were measured from the first postoperative day, at 8 a.m. each consecutive day until gentamicin was no longer measurable. 2 mg/L gentamicin in serum was used as a toxicity reference. The creatinine clearance was calculated according to the Cockcroft-Gault formula (1976).

Results

After a mean of 2 (2–10) days, serum levels of gentamicin could no longer be measured. Toxic gentamicin levels (mean 4.2 (3–13) mg/L) were found 7 times in 7 patients, 1 to 10 days after surgery. In 10 of the 12 patients, a decrease in creatinine clearance was seen in the direct postoperative phase. At final follow-up (mean 13 (2–42) months), 9 patients still showed a decrease in creatinine clearance (mean 10 (5–33) mL/min.) (Table 2).

In patient number 10, it took 10 days before gentamicin could no longer be measured. This particular patient suffered from terminal renal failure and was also the patient who had received 6 sponges

(Table 2). In 3 patients (2, 3 and 4 in Figure 1), the decrease in creatinine clearance was more than 2 standard deviations. In one patient (4), any future antibiotic doses must be adjusted to the decreased renal clearance. In the remaining 3 patients, the renal function has normalized.

Discussion

We have found high serum levels of gentamicin after local use of gentamicin sponges. This is partly due to a quick release of the gentamicin from the carrier. Sørensen et al. (1990) described a half-life of 1.5 h in a laboratory setting. During clinical observations, peak concentrations in drain, serum and urine samples have been found at 2–6 h, with levels that were no longer measurable after 24–48 h (Cyba-Altunbay and Marx 1988, von Hasselbach 1989, Blanc 1992, Letch et al.1993). The numbers of patients described in these studies were low, and the groups were heterogeneous.

The amount of gentamicin introduced locally is known, but it is unknown how much of it is absorbed by the local soft tissues and bone. The absorption depends on local tissue characteristics such as the type of tissue, the wound surface, the degree of vascularization, and the pH. A drain was used in the studies mentioned above. This drainage may account for a variable amount of gentamicin elimination. No drains were used in our study.

No pharmacokinetics of locally administered gentamicin in sponges are described in "Informatorium", the pharmacotherapeutic guidelines of the Netherlands released by WINAp (Wetenschappelijk Instituut voor Nederlandse Apothekers, the Scientific Institute of Dutch Pharmacists); nor could we find any literature on the pharmacokinetics of locally administered gentamicin. It is well known that the elimination of the gentamicin from serum depends on renal clearance.

We found toxic serum levels after such local administration of gentamicin. A persistent decrease in renal clearance was found in some patients. Although only 12 cases were studied, the results were so alarming that we have reduced the number of sponges used for this purpose.

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No competing interests declared.

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