Digoxin Assays: Frequent, Substantial, and Potentially Dangerous Interference by Spironolactone, Canrenone, and Other Steroids

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**Background:** A case of digoxin toxicity resulted from falsely low values with the MEIA II assay for digoxin (AxSYM®; Abbott). The low results were caused by negative interference from canrenone and spironolactone, the latter of which has recently been advocated for the treatment of severe heart failure. Analytical interference from spironolactone has been reported, but little information is available for this effect with newer digoxin assays.

**Methods:** We examined nine assays (AxSYM, IMx®, TDx®, Emit®, Dimension®, aca®, TinaQuant®, Elecsys®, and Vitros®) for interference by spironolactone, canrenone, and three metabolites. Additionally, all routine digoxin measurements (AxSYM) over a period of 16.5 months (n = 3089) were monitored for interference.

**Results:** Suppression of the expected values by canrenone (3125 μg/L) was observed for the AxSYM (42% of expected value), IMx (51%), and Dimension (78%) assays. A positive bias was observed for the aca (0.7 μg/L), the TDx (0.62 μg/L), and the Elecsys (>0.58 μg/L). Twenty-five of 669 routinely monitored patients had falsely low results. Nineteen of these had potentially toxic concentrations of digoxin (Emit; >2.0 μg/L), although the AxSYM assay indicated therapeutic or less severe toxic concentrations (Δmax = 7.1 μg/L). Except for two unresolved cases, this was attributable to spironolactone, canrenone, hydrocortisone, or prednisolone. Standard doses of spironolactone (up to 50 mg/day) in patients with heart failure displayed inhibition <11%.

**Conclusions:** The frequency and magnitude of the false-negative results particularly compromise the use of both microparticle enzyme immunoassays. Not only may toxic concentrations remain unidentified, but intoxication could occur should dosage be increased because of falsely low results. With 11 million digoxin tests/year ordered in the US, conceivably many patients could be adversely affected.

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Despite declining use in the last few years, digoxin is still one of the most frequently prescribed drugs; it was listed twice among the top 200 prescriptions in the US in 2000 (ranking 36 and 194) (1). In 1995, it was the drug most often monitored therapeutically, with ~11 million tests in the US (2) because of its narrow therapeutic window and potentially serious side effects. Recently, a case of intoxication was reported after the administration of high doses of digoxin (3). Increased dosing had been prompted by continual falsely low serum digoxin concentrations with the AxSYM® (Abbott) microparticle enzyme immunoassay (MEIA II).1 Spironolactone and canrenone were identified as the major interfering substances. The patient had received digoxin to normalize his heart rate, as well as potassium canrenoate (K-canrenoate), a prodrug of canrenone, for the treatment of ascites.

K-canrenoate is available throughout Europe and in the United Kingdom but not in the US because of its alleged carcinogenic potential (4). According to the package insert for Aldactone-Ampullen® (Roche), K-canrenoate is recommended in doses of up to 800 mg/day for primary and secondary hyperaldosteronism and for the treatment of ascites if a rapid response to therapy is needed or if oral therapy is not possible because of disturbed consciousness or absorption (e.g., portal hypertension). Oral spironolactone is available worldwide and is recommended in doses of up to 200 mg/day for the treatment of edema in congestive heart failure, hepatic

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1 Nonstandard abbreviations: MEIA, microparticle enzyme immunoassay; ICU, intensive care unit; and DLIF, digoxin-like immunoreactive factor.
carrhidosis, or nephrotic syndrome. Doses up to 100 mg/day are recommended for the treatment of essential hypertension and hypokalemia, whereas doses up to 400 mg/day are suggested for functional testing and diagnosis of primary hyperaldosteronism (package insert for Aldactone®; Searle).

As this case of digoxin toxicity was being reported, a large clinical study was terminated early because of a 30% drop in the mortality rate of patients with severe heart failure who received spironolactone (5). Seventy-five percent of these patients had also received digoxin. On the basis of the findings of this clinical study, there could be a substantial increase in the number of potentially affected patients because both spironolactone and digoxin could be given for the same condition.

In digoxin assays, positive interference by spironolactone and canrenone, an active metabolite of spironolactone and K-canrenoate (for intravenous application), has been described previously (6–8), but little information is available for newer automated assays (9, 10). To our knowledge, there are no published data concerning the frequency of concomitant therapy of digoxin and spironolactone or K-canrenoate and the possible frequency and significance of this interaction in digoxin monitoring. We therefore tested nine available digoxin assays for interference with spironolactone, canrenone, and three major metabolites and assessed whether the recommended low doses for patients with severe heart failure produce noticeable interference. To determine the significance and frequency of this interaction in a clinical setting, all routine digoxin measurements with the AxSYM MEIA II assay were monitored for interference, and the cause of interference was verified where possible.

**Materials and Methods**

The following digoxin methods were performed as suggested by the manufacturers: AxSYM MEIA II; IMx® MEIA II (singleton analyses; Abbott); TDx® fluorescence polarization immunoassay (FPIA; singleton analyses; Abbott); Emit 2000® (Dade Behring) on the Cobas Mira S system; Dimension® (Dade Behring); aca® (Dade Behring) on the aca SX (singleton analyses); TinaQuant® (Roche) on the Hitachi 912; Elecsys® (Roche) on the Elecsys 2020; and Vitros® slides (Ortho Clinical Diagnostics) on the Vitros 950. Presented results are the means of duplicate measurements unless otherwise specified.

For in vitro experiments, a drug-free serum pool was supplemented with various concentrations of digoxin (98.6% pure; Sigma) and spironolactone (Sigma), canrenone, 7-thiospirolactone, 7-thiomethylspirolactone, or 6-hydroxy-7-thiomethylspirolactone at concentrations of 98, 391, 1563, 6250, and 25 000 µg/L (canrenone and its metabolites from Searle, Skokie, IL). In a separate experiment, the serum pool was supplemented with digoxin and dexamethasone, prednisolone (both from Merck), methylprednisolone (Hoechst), or hydrocortisone (Pharmacia & Upjohn) at concentrations of 50, 250, 500, 2000, 10 000 and 40 000 µg/L.

Ultratiration experiments were performed with Centrifree® 30-kDa filters from Amicon. Ultratiltration was carried out by centrifugation at 3500g for 20 min.

For serum samples from patients undergoing therapy (25–400 mg/day) with spironolactone (oral) or K-canrenoate (intravenous) but not digoxin, the recovery of added digoxin in vitro was determined with the AxSYM, Emit, and TDx assays. After receiving approval from the local institutional committee on human research and obtaining informed consent from all patients, we collected extra serum samples for in vitro experiments.

For some samples, HPLC analysis of spironolactone, canrenone, and 7-α-thiomethylspironolactone was carried out by BioKinet GmbH. All routine digoxin measurements with the AxSYM MEIA II assay were performed both undiluted and in a 1:1 dilution (Abbott line diluent) over a period of 16.5 months (October 1, 1999, to February 15, 2001). Discrepant results (>0.2 µg/L difference between native sample and corrected dilution) were verified by measurement with an alternative method confirmed to be free of interference from spironolactone and canrenone at therapeutic concentrations (Emit). Suspected treatment with spironolactone, K-canrenoate, or other possible interferents was confirmed by subsequent inquiry on the ward and evaluation of the patients’ files.

External quality control was ensured through participation in the German proficiency testing scheme (IN-STAND, Düsseldorf). During the study, the maximum deviation from target concentrations was 9%, with an average of 4.3% (mean bias, 2.8%). The results of internal quality-control assessments are shown in Table 1.

**Results**

**IN VITRO EXPERIMENTS**

Minimal or no interference was observed for the Vitros slides, the TinaQuant assay, and the Emit assay when various concentrations of spironolactone, canrenone, and the three metabolites had been added to drug-free serum or drug-free serum supplemented with digoxin to a final concentration of 3.86 µg/L. By contrast, variable positive

| Table 1. Total imprecision of our routine (AxSYM) and comparison (Emit) methods for digoxin, calculated from control samples. |
|---|---|---|---|
| Control sample | CV, % | Mean, µg/L | Target, µg/L |
| AxSYM | Low | 7.4 | 0.87 | 0.90 |
| Medium | 5.5 | 1.89 | 1.90 |
| High | 4.9 | 3.24 | 3.20 |
| Emit | BioRad I | 12 | 0.70 | 0.67 |
| BioRad II | 6.5 | 1.76 | 1.81 |
| BioRad III | 4.3 | 3.22 | 3.0 |
or negative interference was observed in the other assays, particularly when canrenone had been added. This was also observed to a lower degree with spironolactone, 7-thiospirolactone, and 7-thiomethylspirolactone (Fig. 1, A–D, and Fig. 2, A–D).

Falsely increased digoxin concentrations could be detected with the aca and TDx, mainly in the absence of digoxin, and with the Elecsys, mainly when digoxin was present. The strongest positive bias was caused by canrenone, starting at concentrations of ~400 μg/L (Figs. 1B and 2B). At 3125 μg/L, the approximate serum canrenone concentration for the patient reported (3), the bias could be estimated as 0.7 μg/L (aca), 0.62 μg/L (TDx), or >0.58 μg/L (Elecsys in the presence of digoxin; Figs. 1B and 2B).

Falsely low readings were observed for the Dimension (78% recovery at 3125 μg/L canrenone) and both MEIA assays (recovery, 42% with the AxSYM and 51% with the IMx assay; Fig. 2, A–D). These false-negative results were noticeable starting at canrenone concentrations of 100 μg/L (Fig. 2B).

Fig. 1. Apparent digoxin concentrations in the presence of spironolactone (A), canrenone (B), and three major metabolites (C–E), all added in vitro to drug-free serum.

No digoxin was present.
The extent of inhibition of the AxSYM MEIA assay increased not only with the concentration of canrenone but also with the concentration of digoxin (Fig. 3).

**Patients Receiving Spironolactone or K-Canrenoate, but Not Digoxin**

The concentrations of spironolactone, canrenone, and 7-α-thiomethylspironolactone were measured (BioKinet) in 24 serum samples from eight patients undergoing therapy with spironolactone or K-canrenoate. Five serum samples originated from two patients who were receiving digoxin as well. Spironolactone was below the detection limit of 15 μg/L in 19 of the 24 samples (31–104 μg/L in the other 5 samples). 7-α-Thiomethylspironolactone concentrations ranged from 46 to 371 μg/L in 17 samples and were below the limit of detection (15 μg/L) in 7 samples. The highest concentrations were found for canrenone (36–3949 μg/L). Fig. 4 shows the correlation between the log of the measured canrenone concentration and the recovery of the AxSYM digoxin assay.

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**Fig. 2.** Apparent digoxin concentrations in the presence of spironolactone (A), canrenone (B), and three major metabolites (C–E), all added in vitro to drug-free serum.

All samples were supplemented with 3.86 μg/L digoxin. Elecsys assay results reported as >5 μg/L are depicted in the plots as 5 μg/L (A–D).
Sera from 10 patients [7 from the gastroenterology department and 3 from the anesthesiology intensive care unit (ICU)] receiving 100–600 mg of K-canrenoate per day, mostly for the treatment of ascites as a consequence of cirrhosis of the liver, were tested for interference in the AxSYM assay. Digoxin-like immunoreactive factor (DLIF) is often present in such patients and has been reported to suppress MEIA results \(^{(11, 12)}\) and cause a positive interference in the Emit assay \(^{(13)}\). Several other studies, however, have not been able to reproduce the latter findings \(^{(14–16)}\). Before digoxin was added, there was no Emit result in excess of 0.5 \(\mu\)g/L, indicating that the strong inhibition of the AxSYM assay observed after the addition of digoxin was primarily attributable to the presence of canrenone and not DLIF (recovery, 35–81%; total mean, 60%). The observed inhibition of the AxSYM assay in these 10 patients increased with higher doses (100, 200, 400, and 600 mg) of K-canrenoate per day (recoveries, 63.3% for 100 mg/day; 61.4% for 200 mg/day; 59.8% for 400 mg/day; and 50.8% for 600 mg/day; single results for 100 and 600 mg/day; means for 200 and 400 mg/day).

In one patient who received 100 mg of K-canrenoate intravenously twice a day, blood samples were drawn before dosing as well as 2 and 15 min after dosing and were supplemented with 3.38 \(\mu\)g/L digoxin. The AxSYM assay showed a significant inhibition before dosing (recovery, 56%) that became more pronounced both 2 (43%) and 15 min (47%) after intravenous dosing.

To determine whether the recommended low doses of oral spironolactone for patients with heart failure produce interference, we added digoxin to in vitro serum samples from 12 patients receiving daily spironolactone doses between 25 and 100 mg to achieve a concentration of 3.86 \(\mu\)g/L (9 cardiology and 3 gastroenterology patients). The recovery in the AxSYM assay was lower compared with the control in all but one sample tested. The average recoveries before and 3 h after spironolactone was administered were 90% and 87% for the nine cardiology patients for both samples drawn (difference not significant). For the eight patients receiving 25 or 50 mg/day, the respective numbers were 92% and 89%. The recovery for the four patients receiving 100 mg/day was 64%.

**Patients Receiving Spironolactone, K-Canrenoate, or Other Interferents and Digoxin**

Ultrafiltration is the standard procedure used to eliminate high-molecular weight interfering substances and to verify unbound digoxin concentrations \(^{(12, 17–21)}\). Despite canrenone being 89.9–98.3% protein bound \(^{(22, 23)}\), the interference in the AxSYM assay could not be eliminated by ultrafiltration because it appeared to be a logarithmic function of canrenone concentrations (Fig. 4). Fig. 5 shows serial dilution and ultrafiltration of serum from the pre-

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Fig. 3: Drug-free serum supplemented with various concentrations of digoxin and canrenone. Samples were measured with the AxSYM MEIA II assay. The graph shows that the extent of inhibition depends on both canrenone and digoxin concentrations.

Fig. 4: Canrenone concentrations measured in 24 samples from eight patients undergoing therapy with spironolactone or K-canrenoate. The correlation between the log of the measured canrenone concentration and the recovery of the AxSYM digoxin assay was calculated relative to in vitro-added digoxin (3.86 \(\mu\)g/L) in those patients not receiving digoxin and relative to the results of the Emit digoxin assay in those samples from patients receiving digoxin.

Fig. 5: Serum sample from a patient (3) treated with K-canrenoate and digoxin diluted 1+1 (1 mL of sample diluted with 1 mL of drug-free serum) with drug-free serum and then ultrafiltered. Both the ultrafiltrate and the unfiltered serum were diluted again to achieve a final dilution of 1+3 (1 mL of 1+1 dilutions diluted with 1 mL of drug-free serum). All specimens were measured with the AxSYM assay and the Emit assay as reference (Emit result of native sample, >5.0 \(\mu\)g/L). Only a small portion of the interferent was removed by ultrafiltration.
viously reported patient (3). Ultrafiltration removed only a fraction of the interference, as can be seen by the increased recovery upon further dilution. Interpretation of the ultrafiltration results was complicated by the fact that it also removes protein-bound digoxin, which accounts for \( \approx 23\% \) of total digoxin (20).

In this study, the identification of canrenone interference in the AxSYM assay was accomplished by diluting the sample, which yielded higher concentrations after correction for dilution (Fig. 5). The procedure was limited by the limit of quantification of the assay and the digoxin concentration in the sample. Minor interference could not be detected this way.

In a period from October 1, 1999, to February 15, 2001, we monitored all routine digoxin measurements with the AxSYM MEIA II assay (3089 samples from 669 patients) for interference with spironolactone or canrenone, using the dilution procedure outlined above. In 25 of 669 monitored patients (3.74%), significant inhibition of the AxSYM assay compared with the Emit assay was observed (Fig. 6). Nineteen of these patients (2.84%) had potentially toxic concentrations of digoxin (Emit result \( > 2.0 \mu g/L \)) despite therapeutic (\( n = 17 \); 2.54%) or less toxic (\( n = 2 \)) concentrations being reported by the AxSYM assay. The maximum difference observed was 11.1 \( \mu g/L \) with the Emit compared with 3.99 \( \mu g/L \) with the AxSYM. All but two of these patients were in intensive care units (three different units run by the internal, surgical, and anesthesiology departments in our tertiary care university hospital). This indicates that 8.15% of all ICU patients being monitored for their digoxin concentrations had falsely low results reported by the AxSYM assay. Most of the patients had received intravenous K-canrenoate doses between 200 and 600 \( mg/day \), but inhibition was also observed at 25 \( mg/day \) K-canrenoate (intravenous), 50 \( mg/day \) spironolactone (oral), and 200 \( mg/day \) spironolactone (oral). In most patients, inhibition could be observed in several samples obtained during therapy.

During the screening for discrepant results, serum samples from three patients showed significant inhibition in the AxSYM assay, despite the fact that the patients were not receiving spironolactone or K-canrenoate. Two of the patients had received hydrocortisone and one had received prednisolone at doses of 96–200 \( mg/day \). Cortisol was measured in both patients receiving high-dose cortisol (hydrocortisone) therapy (Table 2), and the interference of these steroids then verified in vitro. Recovery in the AxSYM assay at 13 000 nmol/L was 72% for hydrocortisone and 81% for prednisolone. No significant interference was observed in the Emit and TDx assays for these interferents, or for methylprednisolone or dexamethasone in any of the three assays.

One patient was reported via telephone as having received K-canrenoate, but this could not be verified in the file (patient 9 in Table 2). The patient died on the day of the discrepant sample. DLIF remains a possible explanation for the suppression of the AxSYM results (11, 12).

Another patient was admitted to the hospital after an attempted suicide with high doses of digoxin, diltiazem, phenprocoumon, and oxazepam, which was verified by quantitative or qualitative analysis. The ingestion of enalapril, trisodium chloride, and a ginkgo biloba preparation (Tebonin intense\textsuperscript{®}; Dr. Wilmar Schwabe GmbH & Co) was also plausible after partly or completely empty packages were found. When digoxin was measured with the AxSYM assay in three samples taken within \( \sim 4 \) h, the AxSYM reported the following results: 3.99, 3.43 and 3.36 \( \mu g/L \). Diluting the first sample with 2 parts of diluent produced a concentration of 9.5 \( \mu g/L \). The corresponding results from the first sample for the Emit, TDx, and aca assays were 11.1, 10.5, and 12.3 \( \mu g/L \) digoxin. In contrast to the AxSYM assay, results from the undiluted sample were reported as being above the upper limits for the assays. After the increased digoxin results were confirmed with various assays and in various dilutions, the patient received anti-digoxin antibody therapy.

According to all available information, this patient had not taken spironolactone, K-canrenoate, hydrocortisone, or prednisolone. Canrenone could also not be detected by HPLC in a pool of the three samples before antibody therapy. Cortisol was increased both in a pool of the three samples before initiation of digoxin antibody therapy (1148 nmol/L) and after treatment (1093 nmol/L), possibly because of stress in connection with the attempted suicide. However, the concentrations found do not explain the extent of inhibition observed. Because the cortisol assay used (Elecsys\textsuperscript{®}; Roche) shows a \( > 100\% \) cross-reactivity for prednisolone, both hydrocortisone and prednisolone could be ruled out as causing the observed inhibition. In vitro testing for interference from any of the medications the patient had taken in the suicide attempt...
failed to explain the strong inhibition of the AxSYM assay. Other medications that had been previously ruled out as inhibitors when the first case of canrenone inhibition was investigated (3) were metamizol, distigmine bromide, norfenefrin, ciprofloxacin, fluconazole, imipenem, dopamine, adrenaline, heparin, ethacrynic acid, omeprazole, ambroxole, and intravenous preparations of amino acids, lipids, and several vitamins.

DLIF also does not serve as an explanation of the interference in this latter case. The TDx assay, despite being sensitive for positive DLIF interference (24), reported no results in excess of the other methods, nor was a significant portion of the interference removed by ultrafiltration (21). Nevertheless, this patient displayed the greatest analytical inhibition with the potentially most serious consequences observed during the 16.5-month observation period of our study.

Important information about the 25 patients found to have significant inhibition of their digoxin results in the AxSYM assay is summarized in Table 2.

### Discussion

Except for the Vitros slides, the TinaQuant, and the Emit assays, both falsely increased [TDx (9, 10, 25), aca, and Elecsys] and inhibited results (AxSYM, IMx, and Dimension) have to be expected when spironolactone or K-canrenoate and digoxin therapy are combined. The clinically most significant interaction found in this study was the massive inhibition in the MEIA II assays (AxSYM and IMx) followed by a weaker inhibition of the Dimension assay. The overall inhibition observed in vivo is a compound effect of spironolactone, canrenone, and at least two metabolites. All of these showed interference in this

### Table 2. Important clinical data from 25 patients with falsely low digoxin results reported by the AxSYM assay.

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<th>Creatinine, μmol/L (44-115)</th>
<th>Bilirubin, μmol/L (&lt;21)</th>
<th>INR</th>
<th>TP, g/L (60-80)</th>
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*a* Therapeutic and reference ranges in parentheses.

*b* AxSYM 1 + 1 denotes the results of the AxSYM digoxin assay in a 1 + 1 dilution corrected for the dilution.

*c* INR, international normalized ratio; TP, total protein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Tox, toxicology; IV, intravenous; ICU, internal ICU; ND, not determined; SICU, surgical ICU; AICU, anesthesia ICU; Chann, special ward channeling admissions to the hospital.

*d* The wards are run by independent departments and do not share common treatment guidelines.

*e* Patient also received 25 mg/day hydrocortisone.
study and are present at high concentrations in vivo (26, 27).

The amount of positive interference observed in some of the assays will most likely not significantly influence the clinical course of patients affected. Toxic concentrations resulting from positive interference alert both pathologists and clinicians and lead to further investigation, during which interference should be detected. At worst, interference leads to the administration of insufficient digoxin dosages.

Negative interference, particularly in the magnitude observed in both Abbott MEIA II assays (AxSYM and IMx), is much more dangerous. Toxic concentrations may remain unidentified or toxicity could occur should dosing be based on such misleading low values (3). Supposedly “normal” therapeutic concentrations are measured when the true concentration is much higher. Unless all samples are diluted or cross-checked with another method that is insensitive to the interference, there is no indication for the laboratory that the results are incorrect.

In cases where simultaneous treatment with aldosterone inhibitors is reported or known, ultrafiltration of the sample can only partly remove the inhibition and does not lead to a correct result.

A hypothetical mechanism for the inhibition of the MEIA II assay has been described based on the assumption that the cross-reactant dissociates from the antibody during the wash step and allows greater binding of the tracer to the available antibody sites (11). Considering this mechanism, it could be that MEIA assays other than the assay for digoxin also suffer negative interference from cross-reactants known to interfere positively in other assay designs. Similar assay formats should, therefore, be evaluated for this phenomenon. Testing interference in the presence of the primary ligand is mandatory (11).

Which doses are needed to produce a significant suppression of the AxSYM digoxin assay? This study shows that canrenone concentrations reached during conventional ascites therapy (100–600 mg/day K-canrenoate or spironolactone) will most likely cause significant inhibition (recovery, 64% at 100 mg/day). DLIF adds to the problem because it has also been reported to inhibit MEIA assays (11) and to be present in end stage liver disease (28–32), a condition prompting the use of high-dose spironolactone for ascites therapy.

The lower doses recommended for patients with heart failure (12.5–50 mg spironolactone/day) usually translate into inhibition <11% (recovery >89%). The number of patients possibly affected by this limited inhibition is significant because spironolactone therapy has been advocated for the therapy of severe heart failure (3) and 75% of patients in that study had also received digoxin. The observed inhibition could be greater in individual cases because outpatients are often told to delay their digoxin dose when therapeutic drug monitoring is planned, creating a situation where samples for digoxin concentration monitoring are drawn during the peak concentrations of spironolactone.

Another clinically important finding of this study is the negative interference from compounds other than aldosterone inhibitors. Despite the fact that most immunoassays routinely used to measure digoxin have reasonably low cross-reactivities with the known physiologic hormones (<1%) (2), positive interference has been reported with therapeutically given steroids such as hydrocortisone (33), prednisolone, and other synthetic steroids (34). It could, therefore, be possible that the MEIA II assays are also sensitive to steroids or steroid-like compounds other than hydrocortisone and prednisolone.

Apart from steroids, weaker negative interference for the AxSYM assay has been reported for digitoxin, bufalin (a cardioactive component of the Chinese medicines Chan Su and Lu-Shen-Wan), and oleandrin, a compound not in clinical use (11, 12, 21, 35, 36).

More concerns were raised by the unresolved case of suicidal intoxication. This case illustrates the possible consequences of falsely low digoxin measurements for the adequate therapy of patients with true digoxin toxicity. Antibody therapy would have not been initiated based on digoxin results <4 μg/L as opposed to the reported concentration of 11.1 μg/L.

How many patients are clinically affected? In this study, digoxin concentrations measured with the Abbott AxSYM assay were falsely low in 3.74% of patients (8.15% of ICU patients) in a tertiary care setting mainly because of canrenone (37), hydrocortisone, and prednisolone. Three of four of these patients had potentially toxic concentrations when the AxSYM assay actually reported therapeutic concentrations or greatly underestimated the extent of toxic concentrations. Subsequent action and reporting of the correct higher results ensured that the current digoxin dose was stopped, paused, or reduced. In a routine setting where this interference is not recognized, one must assume that the affected patients would develop even higher digoxin concentrations than reported here. This could be the result of continuation of standard doses despite unrecognized toxic concentrations, or even increased dosing based on falsely low, subtarget concentrations.

Because of our limited screening strategy, probably more patients than were discovered here, in particular those treated with lower doses, were affected by less pronounced falsely low results with the AxSYM assay. It is important to note that, despite repeated instruction, we could not rely on concurrent spironolactone or K-canrenoate therapy being reported when digoxin monitoring was requested in our hospital.

In conclusion, this study shows beyond the previous case report on negative canrenone interference (3) that:

- Interference from aldosterone inhibitors is a potential problem in an alarmingly high number of patients, in
particular intensive care patients, and is not confined to single, difficult cases (38)

• Several modern digoxin assays suffer from positive or, in particular, potentially dangerous negative interference from aldosterone inhibitors

• Aldosterone inhibitor doses much lower than in the reported case (3) cause significant suppression of digoxin results in the MEIA II assays

• Low cardiologic doses of aldosterone inhibitors produce limited inhibition only

• High-dose hydrocortisone, prednisolone, and other as yet unidentified compounds also cause extensive falsely low digoxin readings in the MEIA II assays

We thank Searle (Skokie, IL) for providing canrenone and its metabolites, Heumann Pharma for supporting the measurement of spironolactone and its metabolites by BioKinet GmbH (Vienna, Austria), and all of our colleagues who helped with the collection of samples.

References


