Good Clinical Outcome After Accidental Intra-arterial Injection of Flunitrazepam Tablets in 16 Drug Abusers with Critical Limb Ischaemia

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WHAT THIS PAPER ADDS
There have only been a few studies published on the treatment of inadvertent intra-arterial injection of dissolved tablets containing sedatives, such as flunitrazepam, with - in part - unsatisfactory clinical results. Here, we report on the good outcome of 13 out of 16 drug abusers who had injected themselves intra-arterially with flunitrazepam leading to critical limb ischaemia. Treatment according to a standardized protocol prevented irreversible tissue damage in 14 out of 16 patients, even when delayed treatment. As the general outcome was improved and adverse effects or therapy-associated complications were not observed, this protocol is suitable for clinical practice.

Objectives: Inadvertent intra-arterial injection of flunitrazepam tablets intended for intravenous use by drug abusers has devastating effects. We report here on the clinical outcome of 16 drug abusers developing critical limb ischaemia after flunitrazepam injection.

Methods: Treatment combined immediate analgesia and anticoagulation, long-lasting local thrombolysis and vasodilatation, antibiotic prophylaxis, and physical mobilization. The immediate bolus injection of 5,000 IU heparin was followed by a continuous heparin infusion up to the target partial thromboplastin time. Under arteriographic control local intra-arterial infusion with alternating 4-h cycles of 5 mg recombinant tissue plasminogen activator followed by 5 mg prostaglandinE1 (PGE1) was performed for 24—48 hours. Subsequently, 60 μg PGE1 was applied once daily.

Results: Drug abusers, having been injected with 4—30 mg flunitrazepam, were treated 3—72 hours after the accident, with six of them not being treated until after 24 hours. All showed a high tissue ischaemia score. At the time of being discharged from hospital 13 patients had a normal extremity. In one patient, first receiving treatment 72 hours after injection, minor amputation of fingers was necessary. The life of the patient who injected 30 mg flunitrazepam in the leg was saved after hip disarticulation. One patient developed neurological dysfunction in the affected toes.

Conclusions: Intensive treatment after inadvertent intra-arterial drug injection normalized the affected extremity in most drug abusers, even after the late onset of therapy.

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INTRODUCTION

The misuse of drugs for recreational purposes has increased the number of inadvertent intra-arterial injections of crushed, dissolved tablets containing sedatives or narcotics, which often results in critical limb ischaemia, culminating in the risk of limb amputation. Flunitrazepam, a benzodiazepine also known as narcozep, rohypnol, or primum, is abused to reduce the stimulant effects of cocaine, and in combination with heroin to enhance the effects of the drug and to ameliorate withdrawal.1—3 Flunitrazepam is prescribed in Europe and Latin America for the treatment of insomnia and as a pre-anaesthetic medication, but has not been approved in the USA. In Germany it was scheduled under the narcotic drugs act to decrease misuse in 2011.

Intra-arterial injection of crushed, dissolved tablets containing multiple constituents, such as microcrystalline cellulose or magnesium stearate, by drug abusers leads to adverse effects on blood flow and the vascular endothelium. Additionally, the tablets are invariably contaminated with impurities when procured illegally. In contrast to iatrogenic intra-arterial drug injection, after inadvertent intra-arterial injection in drug abusers much more time is lost...
until effective therapy, thus increasing the risk of critical limb ischaemia. Early diagnosis of the ischaemic syndrome followed by an immediate effective therapy is essential for complete limb rescue.

Only case studies on the treatment of inadvertent intra-arterial injection of flunitrazepam tablets have been published so far.4–9 A literature search revealed that a generally accepted treatment algorithm for accidental intra-arterial drug injection to stop critical limb ischaemia is missing. A variety of substances and therapies, and their combinations, has been used. Anticoagulation and vasodilation,5,10–13 and/or local fibrinolysis6–9,14,15 are integral parts of many treatment protocols. Haemodilution with low molecular weight dextran,11,16 continuous plexus blocks and regional nerve blocks for sympathicolysis,13,17 and corticosteroids5,16 are also often applied, whereas sympathetic antagonists18 and hyperbaric oxygen therapy combined with antiplatelet agents5 have rarely been used. The small number of patients involved in most of these empiric studies made it difficult to develop an effective well-accepted treatment protocol.

The objective of this study is to report the outcomes of patients after inadvertent intra-arterial injection of flunitrazepam tablets, and suffering subsequent critical limb ischaemia, after treatment according to a novel standardized protocol.

PATIENTS AND METHODS

Patients

The retrospective study included drug abusers with critical limb ischaemia following accidental intra-arterial injection of dissolved flunitrazepam tablets who were admitted to the emergency ward of the Vascular Surgery Unit, University of Leipzig, within a 36-month period before 2011. After this period admissions of such patients to this hospital stopped, probably because flunitrazepam was scheduled under the narcotic drugs act in 2011.

As we combined common clinical routine steps, the treatment regimen did not need ethical approval.

Diagnosis

After admission to the hospital, the patients’ histories were taken. Motor and sensory deficits of the injected extremity were measured using sharp—dull or two-point discrimination. Missing sensory function was judged as abnormal. The colour and temperature of the injected extremity were assessed. Cyanotic and cool/cold limb were judged as abnormal. Pulses of the common femoral, popliteal, and anterior/posterior tibial arteries, as well as of the brachial and radial/ulnar arteries, were assessed—if the drug was injected into the leg or arm—by high-resolution colour-coded duplex sonography. Capillary refill was assessed at the most distal extent of injury. A time delay of more than 3 seconds was judged as abnormal. In summary, a tissue ischaemia score, including the four assessed clinical signs of sensory function, colour, temperature, and capillary refill of the affected extremity, was used to judge ischaemic injury.16 Each sign was scored either normal (= 0) or abnormal (= 1), and then they were summed up to provide the tissue ischaemia score in the range of 0 to 4. The score was established by Treiman et al.16 Until now this score could not be validated because of the low number of patients that was included in studies that were published subsequently.

After taking the patient’s medical history and first diagnosis, a high-dose analgesia with 7.5—15.0 mg piritramide (Dipidolor; Janssen-Cilag, Neuss, Germany) was promptly injected intravenously (i.v.). Next, each patient received detailed information on the clinical consequences of intra-arterial tablet injection and on further treatment.

Dependent on the affected extremity, transfemoral or transbrachial arteriography with a 5-F introducer set was performed in each patient, at first for further diagnostic analysis, and, second, to initiate local thrombolysis with recombinant tissue plasminogen activator (rt-PA) in the affected extremity. Arteriography was carried out using a Siemens Artis zeego multi-axis System (Siemens Deutschland, Munich, Germany).

Treatment regimen

Owing to the fact that therapeutic guidelines are still missing, we established an intensive treatment protocol based on published data on inadvertent intra-arterial injection of dissolved flunitrazepam and other tablets or gels. The protocol is summarized schematically in Fig. 1.

Well-accepted single therapeutic interventional and conservative steps consisting of analgesia, anticoagulation, vasodilation, local thrombolysis, antibiotic prophylaxis, and physical mobilization were combined. Directly after detailed information had been provided to the patient and diagnostic arteriography, the following treatment algorithm was applied:

1. Anticoagulation was started by an i.v. bolus application of 5,000 IU heparin (Liquemin; Roche-Pharma, Grenzach-Wyhlen, Germany), followed by continuous heparin infusion i.v. until partial thromboplastin time was 2.0—2.5 times higher compared with control value.
2. To fibrinolysis local thrombi in the affected limb and to prevent systemic thrombosis, a 4-h local intra-arterial infusion of 5 mg rt-PA (Actilyse; Boehringer-Ingelheim Pharma, Ingelheim, Germany) was alternated with a 4-h intra-arterial application of 5 µg prostaglandin E1 (PGE1) (Prostavasin; Schwarz Pharma, Monheim, Germany). These 4-h cycles were continued over 24—48 hours. Arteriographic control was performed for the first time 24 hours after beginning fibrinolytic therapy and was repeated every 12 hours until the occluded vessels were free. If there was no improvement seen by arteriography at the 48-hour time point, intra-arterial fibrinolytic therapy was stopped.
3. To maintain the vasodilator effect the therapy was continued with 60 µg PGE1 once daily i.v. up to discharge from the hospital.
4. Antibiotic prophylaxis with cefuroxime was administered 3 × 1.5 g i.v. daily (Cefuroxim; Ratiopharm, Ulm, Germany) to prevent infection in the ischaemic tissue after the unsterile technique of self-injection.19

5. Sufficient elevation of the affected extremity and early physical therapy, to reduce oedema and minimize stasis and the development of contractures or residual motor deficits of the affected extremity, are further therapeutic measures. Passive mobilization was applied immediately after the bolus injection of heparin (three times daily, 20–30 minutes each). Active physiotherapy was started after finishing the intra-arterial fibrinolytic therapy and was also applied 2–3 times daily.

Statistics
For all parameters median and interquartile range [25th–75th percentile] were used.

RESULTS

Clinical examination of the patients
Table 1 summarizes the clinical and anthropometric characteristics, treatment, and outcome of patients. The 16 patients (aged 24.0 [20.0–36.0] years old), sought medical advice after 20 [5–32] hours. In 6/16 patients this was more than 24 hours after accidental injection.

The clinical picture of intra-arterial injection of crushed tablets is very typical. After taking the patient’s medical history, a wrong diagnosis is impossible. All patients noted a sudden excruciating burning pain with increasing intensity immediately after intra-arterial injection of flunitrazepam in the affected extremity. At admission, these extremities were swollen and appeared cyanotic in all patients, and the limb skin was mottled blue or blue-green distal to the injection site. The tissue ischaemia score ranked between 3 and 4. In 13 out of 16 cases the occlusion was purely microvascular. Here, the distal pulse in the affected limb was normal or accentuated by the outflow block. Pulses were absent in three cases. There were no pulses femoral and below in patient 4, who had injected 30 mg flunitrazepam. The other two patients, who arrived at the hospital 48 and 72 hours after injection, had partial pulse defects in the affected limb. All patients developed an oedema, which may increase compartment pressure and has a deleterious effect on the tenuous microcirculatory haemodynamics. All patients had motor and sensory deficits in the affected limb.

The patients injected dissolved flunitrazepam tablets containing 6.0 [4.5–8.0] mg of the active agent. In one case, 30 mg flunitrazepam was applied. The tablets were crushed and dissolved in tap water.

Treatment

Piritramide analgesia was the immediate standard analgesic therapy; other forms of opiates were not tested. This drug shows a very good and fast analgesic effect, and could be injected subcutaneously or i.v. during therapy. After analgesia and providing detailed information on the risks of critical limb ischaemia and further treatment, acceptable compliance was achieved in all patients under therapy.

The alternating intra-arterial cycling therapy with rt-PA and PGE1 infusions was applied for 36.0 [24.0–36.0] hours until patients had a resolution of symptoms yielding a normal extremity, or until a stable morphological or neurological deficit. The tip of the catheter for fibrinolytic therapy and heparin infusion was always localized in the area of occlusion. In patients with accidental injection into the brachial/radial artery, the catheter was introduced retrograde into the femoral artery. In patients with an affected lower extremity the catheter was introduced antegrade into the femoral artery of the same site. A crossover technique was only applied in patient 4, that is the catheter was introduced into the femoral artery of the other, unaffected leg. Arteriograms of two typical patients after the injection of dissolved flunitrazepam before and 24 hours after treatment onset are shown in Fig. 2.

Even after a delay of 48 hours between accident and treatment onset, patency of the occluded arteries was achieved.

None of the patients, except patient 4, were monitored in an intensive care unit. However, during locoregional fibrinolytic therapy, electrocardiogram, pulse, blood pressure, and oxymetry were recorded continuously.
Table 1. Clinical and anthropometric characteristics, treatment, and outcome of patients after inadvertent intra-arterial injection of dissolved flunitrazepam.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Injected artery</th>
<th>Injected flunitrazepam (mg)</th>
<th>Time to treatment (h)</th>
<th>Tissue ischaemic score</th>
<th>Pulse*</th>
<th>Compartment syndrome</th>
<th>Duration of local thrombolysis, intra-arterial PGE1 (h)</th>
<th>Hospitalization (d)</th>
<th>Surgical intervention</th>
<th>Outcome</th>
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<td>24</td>
<td>6</td>
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<td>4</td>
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<td>4</td>
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<td>7</td>
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<td>4</td>
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<td>48</td>
<td>14</td>
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<td>35</td>
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<td>30</td>
<td>18</td>
<td>4</td>
<td>A-/P-</td>
<td>+</td>
<td>24</td>
<td>31</td>
<td>b</td>
<td>Limb amputation</td>
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<td>6</td>
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<td>U+/R+</td>
<td>—</td>
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<td>6</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
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<td>Brachial</td>
<td>6</td>
<td>32</td>
<td>4</td>
<td>U+/R+</td>
<td>—</td>
<td>36</td>
<td>9</td>
<td>—</td>
<td>Normal</td>
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<tr>
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<td>Femoral</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>A+/P+</td>
<td>—</td>
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<td>7</td>
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<tr>
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<td>72</td>
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<td>—</td>
<td>48</td>
<td>28</td>
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<td>Minor amputation</td>
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<td>24</td>
<td>3</td>
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<td>25</td>
<td>Femoral</td>
<td>6</td>
<td>48</td>
<td>4</td>
<td>A-/P+</td>
<td>—</td>
<td>36</td>
<td>7</td>
<td>—</td>
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<td>Brachial</td>
<td>31</td>
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<td>3</td>
<td>U+/R+</td>
<td>—</td>
<td>36</td>
<td>11</td>
<td>—</td>
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<tr>
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<td>Femoral</td>
<td>8</td>
<td>26</td>
<td>4</td>
<td>A+/P+</td>
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<td>Femoral</td>
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<td>A+/P+</td>
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<td>M</td>
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<td>Radial</td>
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<td>7</td>
<td>4</td>
<td>U+/R+</td>
<td>—</td>
<td>36</td>
<td>8</td>
<td>—</td>
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</tr>
</tbody>
</table>

Note. PGE1 = prostaglandin E1; U = ulnar; R = radial; A = anterior tibial; P = posterior tibial; + = pulse present; − = pulse absent.

* Arm: U/R artery; leg: A/P artery.

b Thromectomy, fasciotomy, hip exarticulation.

c Distal interphalangeal amputation fingers II–V.
After treatment, 13/16 patients had a normal extremity without morphological and functional alterations. One patient retained a neurological dysfunction: the affected toes were contracted permanently. In two patients surgical interventions were necessary. In the patient who had a time to treatment after injection of 72 hours, distal interphalangeal borderline amputation of fingers II, III, IV, and V was necessary because of tissue necrosis. Amputation was performed after clear tissue demarcation had developed. The patient who injected 30 mg flunitrazepam, that is 15 crushed dissolved tablets, developed an ischaemic compartment syndrome of the affected leg, caused by excessive rhabdomyolysis, and multi-organ failure evolved. In order to save the patient’s life hip exarticulation was necessary.

Although all patients injected the dissolved flunitrazepam tablets in non-sterile conditions, spreading infections and wet gangrene were not observed under antibiotic prophylaxis with cephalosporin. The median duration of hospitalization was 7.5 [6.0–10.5] days.

Complications such as bleeding, pseudoaneurysms, or arteriovenous fistulae were not seen. Only haematomas, not liable to therapy, were induced.

DISCUSSION

Here we report on the good clinical outcome of 16 drug abusers who developed critical limb ischaemia after inadvertent intra-arterial injection of crushed, dissolved flunitrazepam tablets, and were treated with an intensive protocol combining immediate analgesia and anticoagulation, long-lasting local thrombolysis and vasodilatation, antibiotic prophylaxis, and physical mobilization. Even in 4/6 patients who received this therapy later than 24 hours after the accidental drug injection, the extremity returned to normal without any morphological damage or functional adverse effect after treatment.

Compared with other studies, our report includes an unusually high number of patients with inadvertent intra-arterial injection of flunitrazepam. This is caused, in part, by the fact that flunitrazepam was legally available for sale in Europe and Latin America, but was never marketed in the USA, for example, probably because it has no therapeutic advantage over the benzodiazepines presently marketed there, or because of its greater liability for abuse as a date-rape drug compared with other benzodiazepines.1,2 Sixteen patients within a 3-year period is, nevertheless, high for a German city, suggesting its easy, illegal, availability within the catchment area of the university emergency ward during this period.

Overall, we established an intensive treatment protocol that enabled a good clinical outcome in most patients. Only one patient, who, incredibly, had injected 15 dissolved flunitrazepam tablets, developed catastrophic complications. After complete ischaemia in the affected leg resulting in severe rhabdomyolysis and multi-organ failure, amputation of the extremity was the only life-saving option.

In our treatment protocol we first minimized the risk of coagulation by an immediate bolus injection of heparin. The subsequent continuous heparin infusion maintains patent collaterals and capillary microcirculation, inhibits further propagation of thrombi, and prevents thrombosis in small
veins, thereby preventing outflow obstruction, stasis, and occlusion of the distal arteries.\cite{13,14} High-resolution colour-coded duplex sonography is useful to define the extent of injury at treatment onset.\cite{5,15}

Patients’ compliance was improved by (i) immediate adequate analgesia because the excruciating severe ischaemic pain decreases further the poor compliance of drug abusers,\cite{7} and (ii) detailed information provided to the patient on the imminent risk of extremity amputation. Consequently, the complete treatment protocol could be carried out in all patients.

Moreover, local thrombolysis and vasodilation by alternating intra-arterial infusion of rt-PA and PGE1 was continued until success or unchanged arteriographic result. The combination of both substances stops the pathophysiological cascade and ischaemic process.\cite{6,7,14,18,20} PGE1 markedly enhances the fibrinolytic efficacy of rt-PA and does so, in part, by inhibiting platelet aggregation.\cite{20} It has its own multiple beneficial effects on circulation.\cite{20,21} Consequently, our combined intra-arterial therapy with heparin and alternating rt-PA and PGE1 shows better therapeutic results—recovery of the affected limbs in 80% of our patients—after peripheral arterial occlusions compared with other treatment protocols, although all patients were admitted with a worse tissue ischaemia score and 6/16 more than 24 hours after accidental injection.\cite{7,12,16}

Treiman et al.\cite{16} treated 48 drug abusers, who had injected 13 different substances in various brachial arteries, by application of heparin, dextran 40, and dexamethasone. A good outcome was achieved only when therapy was started within the first 24 hours after injection. A longer delay in treatment onset resulted in a high rate of borderline amputation, which confirmed other studies showing that early onset of therapy is a major determinant of good clinical outcome.\cite{11,16} Moreover, in the study by Treiman et al.\cite{16} only 50% of the patients had a tissue ischaemia score of 3 or higher, as had all patients in our study. Three patients retained functional deficits and in 11 patients digital amputations were necessary, that is 30% had an unsatisfying clinical outcome, whereas in our study defects remained in only 19% of the patients.

The mechanism of ischaemic injury following intra-arterial drug injection is not completely understood. Direct toxicity of the injected drug to the endothelium,\cite{23} increased sympathetic vasospasm,\cite{24} increased platelet aggregation and acid crystal formation,\cite{25} thromboxane release,\cite{18,26} and particulate emboli\cite{27,28} have been previously discussed as triggering factors for the initial insult. Only a few experimental in vivo studies using the rabbit ear model, which reflects insufficient human vascular anatomy, were performed in the 1980s to examine the intra-arterial effects of tablet constituents.\cite{18,19,26,29} Intra-arterial injection of microcrystalline cellulose, a purified depolymerized form of cellulose that is used as a binder in tablets caused direct toxicity to the endothelium. Venous and venous endothelial injury results in the development of venospasm, venous thrombosis, and, secondarily, transient arterial vasoconstriction in the capillary bed up to the occlusion of arterioles and distal arteries.\cite{13,14,25,30} The capillary pressure increases due to the slowed capillary blood flow with the consequence of fluid transudation into the interstitium causing impaired soft tissue perfusion and ischaemia in the areas concerned.\cite{32} Clinically, these events present as severe oedema followed rapidly by stagnation of blood flow with cyanosis. The development of arterial insufficiency and tissue hypoxia results in temperature loss, progressive neurologic deterioration, and, ultimately, gangrene.\cite{16} Irreversible tissue loss of affected extremities occurs in most untreated patients.\cite{32}

The number of articles describing cases of accidental injection of crushed tablets has decreased. In part, this is owing to re-classification of these drugs as narcotics and to other dosage forms. Flunitrazepam-producing companies changed the tablet composition such as for rohypnol (Roche). They added colouring and agglutinating substances, and a bitter flavour to prevent further misuse as a date-rape drug and as an i.v. narcotic in drug abusers. However, generic drug-producing companies did not implement these obvious requirements.

In summary, our treatment protocol for patients with inadvertent intra-arterial injection of dissolved flunitrazepam tablets was very effective. Interactions between flunitrazepam and the agents given during treatment are unknown or have not been described. Together with standard heparin therapy, the alternating combined intra-arterial treatment with thrombolytic rt-PA and vaso-dilatory PGE1 prevented irreversible tissue damage in most patients without an increased bleeding risk. The application of immediate adequate pain treatment and early mobilization of the affected extremity further increased therapy success. The general outcome, also in late-onset of therapy, was improved and adverse effects or therapy-associated complications were not observed.

The protocol was used only in the clinical situation described because patients who had injected other drugs were not admitted to our clinic. Theoretically, the treatment algorithm is transferrable to every accident involving intra-arterially injected crushed tablets or gels. After accidental clinical intra-arterial injection a less rigid protocol will probably be successful because time delay until treatment will not be as long as it was in our study with drug abusers.

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CONFLICT OF INTEREST

None.

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REFERENCES
