

identification of drugs from diverse pharmacologic/therapeutic classes that may contain pharmacophores relevant to the analysis of structure–adverse effect relationship. In practice, a set of drugs signaling for an adverse event could be the basis for initial screening for possible pharmacophore modeling and structure–activity screens to identify patterns that might be fruitful areas for further scientific research. We encourage further investigation in this area.

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Anaphylaxis to intravenous sinistrin

TO THE EDITOR: Inulin/sinistrin clearance is the gold standard for the determination of glomerular filtration rate (GFR). Sinistrin, an analog of inulin, has better water solubility. Anaphylaxis to intravenous administration of inulin/sinistrin is rarely reported. We report an anaphylactic reaction in a healthy male who received sinistrin.

Case Report. A healthy, 25-year-old male Chinese volunteer participated in a Phase I clinical trial with assessment of GFR by sinistrin (Inutest, Fresenius Pharma Austria, Graz). No atopy or allergies were known from his history. No investigations with inulin/sinistrin had been performed previously. He was not taking any medication and had not received any investigational medication prior to sinistrin.

After an overnight fast, sinistrin 2 g in 45 mL of NaCl 0.9% solution with 100 mg of sodium lactate was administered intravenously. After 4 minutes, dyspnea without stridor and a prickling and itching on neck and face appeared. Angioedema of the lips and symmetrical urticarial erythemas on the patient's head, neck, trunk, and upper extremities were observed.

The infusion of sinistrin was stopped, and oxygen (3 L/min) was administered. Prednisolone 100 mg and dimethindene 4 mg (antihistamine agent) were administered intravenously. An electrocardiogram (ECG) indicated an incomplete right bundle branch block with negative T waves ($V_{1,2}$). U waves appeared in leads $V_{3,5}$ (Figure 1). Hypokalemia (3.1 mEq/L) was measured. After one hour, symptoms subsided and the ECG normalized. After 24 days, skin prick testing for sinistrin was immediately positive (1:1 solution).

Discussion. Our patient's symptoms (generalized urticaria, angioedema, dyspnea) and a positive skin prick test indicated an anaphylactic reaction to intravenous sinistrin. Use of the Naranjo probability scale indi-

cated a probable relationship between anaphylaxis and sinistrin.¹ Bronchospasm and, thus, pulmonary hypertension, leading to acute right ventricular stress, may have caused the incomplete right bundle branch block. Hypokalemia and U waves in the ECG were likely to be due to endogenous epinephrine.

To our knowledge, only one other case of anaphylaxis upon intravenous administration of sinistrin has been reported.² A 45-year-old white patient with Wegener's granulomatosis developed anaphylaxis and cardiorespiratory arrest after administration of bolus intravenous sinistrin (2.5 g in 10 mL of solution). A letter has reported anaphylaxis occurring on oral ingestion of inulin in vegetables and processed foods.³

Other polycarbohydrates used in medicine, such as the plasma expanders dextran, gelatin, and hydroxyethyl starch (HES), have low incidences of anaphylaxis (0.273%, 0.345%, and 0.058%, respectively).^{4,5} Dextran anaphylaxis is caused by circulating dextran-reactive immunoglobulin G found in most adults.⁴ Gelatin may lead to histamine release from mast cells.⁴ The mechanism of HES anaphylaxis is unclear; presumably HES-reactive antibodies preformed in humans do not exist or are extremely rare.^{4,6} There are no known cross-reactivities between these substances and inulin/sinistrin.⁵

Anaphylaxis to intravenous sinistrin in healthy individuals, as in our case, seems to be very rare or underreported. The underlying mechanism of inulin/sinistrin anaphylaxis is still unclear. Skin prick tests suggest that the immediate-type hypersensitivity reaction may be immunoglobulin E-mediated.

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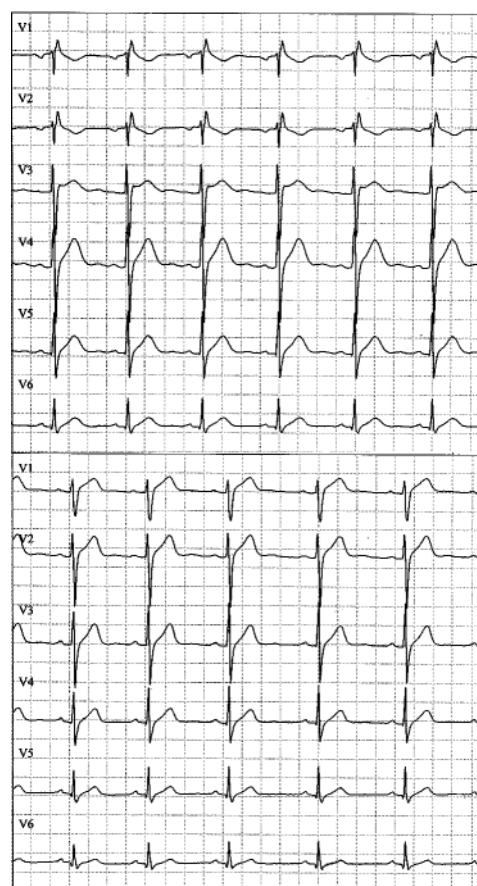


Figure 1. ECG during (upper panel) and after (lower panel) clinical symptoms: incomplete right bundle branch block with negative T waves (V_1 and V_2), U waves in leads $V_{3,5}$.

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Comment: renal protective effects of angiotensin receptor blockers

TO THE EDITOR: Coyle et al.¹ recently prepared an overview of the evidence supporting the nephroprotective effects of angiotensin II receptor blockers (ARBs). They reviewed several large trials comparing ARBs with placebo or active control.^{2,3} Based on these data, ARBs unarguably slow the progression of diabetic nephropathy in patients with and without chronic renal insufficiency (CRI) as evidenced by a reduction in the composite outcome of doubling of the serum creatinine level, development of end-stage renal disease (ESRD), and death. Three matters are worthy of mention with respect to the review. First, patients with diabetic nephropathy are at extremely high risk for future cardiovascular events, including myocardial infarction and cardiovascular death. In fact, cardiovascular events occurred more often than renal outcomes in these trials. ARBs have not been shown to reduce either of these outcomes in a wide range of patients. On the other hand, angiotensin-converting enzyme (ACE) inhibitors are both nephroprotective and cardioprotective, decreasing all major cardiovascular endpoints in high-risk patients.

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.—ED.

Second, evidence emerging after the publication of the 2 largest renal protection trials questions whether ARBs will decrease ESRD in clinical practice.^{2,3} The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study was conducted at 250 centers in 28 countries in Asia, Europe, Central America, South America, and North America. At the end of follow-up, the primary endpoint was reduced by 16%. This reduction was driven largely by a 35% reduction in the Asian population, with smaller, nonsignificant reductions on all other continents. In the IDNT (Irbesartan Diabetic Nephropathy Trial), there was a 20% reduction in the primary endpoint. However, there was no significant difference in progression to ESRD or death, and patients receiving irbesartan suffered a similar number of cardiovascular events as patients who received placebo. The major benefit of irbesartan was its effect on a surrogate endpoint, which was the change in serum creatinine.

Lastly, Figure 1 in the review presents a proposed treatment algorithm for patients with diabetes and microalbuminuria or nephropathy. Step 1 in the algorithm suggests that glycemic control should be addressed first. Blood pressure is considered only after glycemic control has been achieved. This is of concern given the findings from the UKPDS 38 (United Kingdom Prospective Diabetes Study)⁴ and, more recently, the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial.⁵ In the UKPDS, aggressive blood pressure control was associated with reductions in mortality, all diabetes-related events, microvascular disease, and stroke of 18%, 24%, 37%, and 44%, respectively. Conversely, aggressive control of glycemia reduced all diabetes-related events by 12% and microvascular disease by 19%, but did not affect macrovascular disease or death. Furthermore, in the VALUE trial, compared with patients whose blood pressure was lowered to <140/90 mm Hg by 6 months, patients with uncontrolled blood pressure experienced a 21% increase in mortality, 27% increase in cardiovascular events, and 50% increase in cerebrovascular accidents. Consequently, hypertension should receive the bulk of attention since it is expected to have a more profound impact on both micro- and macrovascular disease and because even a minimal delay in adequate control could be detrimental. Blood pressure should be lowered aggressively to <130/80 mm Hg with agents that have been shown to prevent cardiovascular events in this population, namely ACE inhibitors.

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AUTHORS' REPLY: We thank Dr. Epstein for his comments in response to our review of the renal protective effects of ARBs in patients with type 2 diabetes.¹ We would like to address each of his 3 major points.