REVIEW ARTICLE

Drug Safety 2004; 27 Suppl. 1: 11-18
0114-5916/03/0001-0011/$30.00/0

Precautions for Use and Adverse Effects of Vesnarinone

Potential Mechanisms and Future Therapies

Barry D. Bertolet

Cardiology Associates of North Mississippi, Tupelo, Mississippi, USA

Abstract

This article reviews the precautions and adverse effects associated with vesnarinone use, and the potential mechanisms responsible for these complications as well as suggested treatment strategies. Vesnarinone, a quinolinone derivative, improves the haemodynamics and quality of life in patients with congestive heart failure (CHF); however, it is associated with the adverse effects of increased sudden cardiac death and neutropenia. These adverse effects have limited the application of vesnarinone to the general population but perhaps with continued research into vesnarinone-induced neutropenia and advances in arrhythmia management, the risk/benefit ratio of vesnarinone may become favourable. For now, the use of vesnarinone should be limited to patients with CHF who have demonstrated a poor response to other cardiac medications and devices. These patients should be closely monitored for both cardiac and non-cardiac adverse effects.

Vesnarinone (OPC-8212), a quinolinone derivative, was introduced in the late 1980s as a positive inotropic agent for symptomatic left ventricular dysfunction. While vesnarinone improved short-term haemodynamics, congestive symptoms, and quality of life, mixed survival results were noted in the clinical trials.[1-3] Consistent across all the clinical trials, however, was the risk of neutropenia. This article reviews the precautions and adverse effects associated with vesnarinone use, and the potential mechanisms responsible for these complications as well as suggested treatment strategies.

1. Precautions for Vesnarinone Use

Vesnarinone has been primarily studied in symptomatic New York Heart Association (NYHA) class III or IV heart failure patients who have failed conventional heart failure medical therapy, including ACE inhibitors, diuretics, digoxin, and vasodilator therapy. These patients had no acute ischaemic symptoms, overt arrhythmias, or reversible causes of heart failure. After the recognition of agranulocytosis as a possible vesnarinone adverse effect, patients at a higher risk of neutropenia were also excluded from the studies.

The various mechanisms of action of vesnarinone result in a slowing of the heart rate, prolongation of the action potential, and suppression of the delayed outward potassium current. As a precaution, patients receiving β-blockers, antiarrhythmic medications, and those requiring higher dose digoxin, were also excluded from the studies. The exclusion criteria from the larger clinical trials are listed in table I.

Vesnarinone requires the hepatic cytochrome P450 (CYP) system for conversion into its primary metabolite, OPC-18692.[4] While the clinical implications are undetermined, drugs that affect the CYP pathway (table II) should be used with caution. Additionally, vesnarinone and its metabo-

Table I. Vesnarinone trial exclusion criteria

Recent myocardial infarction
Reversible cardiac disease (i.e. postpartum cardiomyopathy)
Recent CABG (within the last 3 months)
History of cardiac arrest
Presence of implantable defibrillator
Significant obstructive valvular or subvalvular disease
Heart rate-slowing medications (digoxin level $>$ 1.8 ng/dl, β-blockers)
Creatinine $>$ 2.4 mg/dl
Treatment with tocainide
Influenza vaccine
History of haematological or immunological disease (drug-induced haematotoxicity, history of drug-induced neutropenia, history of lupus or lupus-like syndrome, neutrophil $<$ 2000/mm^3)

CABG = coronary artery bypass graft.

Table II. Commonly used drugs that affect the cytochrome P450 system pathway

Inhibitors	Inducers
Amiodarone	Phenobarbital
Cimetidine	Rifampicin
Fluoroquinolones	Isoniazid
Ticlopidine	Ethanol
Erythromycin	Carbamazepine
Ketoconazole	
Indomethacin	
Lansoprazole	

lites are eliminated via renal mechanisms. Patients with an elevated creatinine level ($\geq$ 2.5 mg/dl) should not receive vesnarinone, and agents that may worsen renal function should be used with caution.

Vesnarinone inhibits adenosine uptake in endothelial cells, smooth muscle cells, and myocytes.[5] This may provide some cytoprotective effects during episodes of hypoxia and reperfusion;[6] however, in prolonged hypoxic situations (e.g. myocardial infarction), larger amounts of endogenously released adenosine unable to be taken up and metabolised could cause the adverse effects of bradycardia and hypotension. The same effects may also be seen after exogenously administered adenosine (e.g. acute therapy for supraventricular tachycardia, pharmacological myocardial ischaemia stress perfusion imaging).

2. Adverse Effects of Vesnarinone

The adverse effects noted with vesnarinone appear to be dose dependent.[3] The adverse effects attributed to vesnarinone can be divided into two broad categories: cardiac and non-cardiac. The primary adverse cardiac effect noted was an increase in mortality – presumably due to arrhythmogenic sudden death. The primary non-cardiac adverse events noted were diarrhoea and neutropenia.

The increase in cardiac mortality presumably due to arrhythmias caused by vesnarinone was not expected. In animal studies, vesnarinone prolongs the action potential duration and blocks the delayed rectifier K^+ current, which should make it an excellent class III antiarrhythmic agent without the risk of proarrhythmia.[7] Likewise, vesnarinone did not increase the number of premature ventricular contractions (PVCs), as assessed by 24-hour Holter monitoring.[8] Nevertheless, a dose-dependent increase in cardiac mortality was noted with the 60 and 120mg doses of vesnarinone, with no significant change observed with the 30mg dose compared with placebo.[2,3] However, this adverse effect may not be unexpected given the reduced survival rates noted in congestive heart failure (CHF) patients treated with other inotropic agents.[9,10]

It should also be noted that patients with implantable cardioverter-defibrillators (ICDs) were excluded from participation in the vesnarinone trials. It is likely that these devices would have prevented most of the deaths due to a lethal arrhythmia. In light of the growing evidence that ICDs should be considered for all patients with ischaemic- related cardiomyopathy, the adverse cardiac effects of vesnarinone may become less of an issue in the future.[11]

Neutropenia (absolute granulocyte count $<$ 1000/mm^3) with sparing of other cellular lines has been reported in 1–3% of patients receiving vesnarinone. From the initial Japanese experience

(1991–1994), the reported incidence of neutropenia from 14 921 patients who received the drug at least once was <1%.[12,13] The US and European experience from 1984 until 1992 (n = 692) found a composite incidence of neutropenia of 3.18%.[14] A larger US-based multicentre study (n = 3833) found an incidence of 1.2% in patients receiving the 60mg dose and an incidence of 0.2% in those receiving the 30mg dose.[3]

There has been a significant amount of research evaluating vesnarinone-induced neutropenia but no conclusive mechanism has yet been identified (table III). At present, no predisposing risk factor for neutropenia has been found. Most patients develop the neutropenia between 1 and 3 months following first-time exposure (figure 1). Two patients who recovered from vesnarinone-induced neutropenia were rechallenged with the drug; both experienced recurrent neutropenia. There seems to be no relationship between age, sex, or renal function and vesnarinone-induced neutropenia in the US/European trials;[14] however, Japanese women tended to be at a higher risk than Japanese men.[12,13] The large multicentre US trial found a lower incidence of neutropenia at the 30mg dose, suggesting a dose-dependent risk.[3] There is no clear association with the use of concomitant medications, with the possible exception of allopurinol.[14]

The typical bone marrow morphology from the vesnarinone-induced neutropenic patient shows normal or increased megakaryocytes, erythroid hyperplasia, and myeloid hypoplasia and an absence of all maturing forms.[13,14] Vesnarinone may suppress, in a reversible fashion, differentiation of granulocyte-macrophage cells.[16] This effect seemed to be overcome with the addition of granulocyte-macrophage colonystimulating factor (GM-CSF). Adding vesnarinone to stromal cells suppresses the production of GM-CSF, suggesting that vesnarinone impairs normal stromal cell function and prevents the differentiation of more mature myeloid cells.[16,17] Inhibition of granulocyte-monocyte colony-forming unit growth has been observed with vesnarinone concentrations normally noted in the plasma after a vesnarinone 60mg dose.[18]

With regard to cytokine production, vesnarinone plays a role that may benefit patients with CHF. In patients with heart failure, the level of circulating cytokines, particularly interleukin, tumour necrosis factor-α (TNFα), and interferon-γ (IFNγ), are elevated. These cytokines have direct cardiac depressant effects, lower blood pressure, precipitate pulmonary oedema, alter membrane potentials, and cause cardiac cachexia. Vesnarinone inhibits the production of TNFα and IFNγ, which may contribute to the beneficial effects seen in patients with CHF.[18,19] Vesnarinone was shown to inhibit granulocyte-colony stimulating factor (G-CSF) in a patient who subsequently developed neutropenia, suggesting that measurement of cytokines may be useful in predicting the occurrence of neutropenia.[19] Additionally, vesnarinone has been found to cause oxidative damage in myeloid cell lines and induces myeloid apoptosis through inhibition of catalase function.[20] Each of these effects seems more pronounced in leukaemic cell lines, suppressing blast colony-formation and thus making vesnarinone potentially useful in acute myelogenous leukaemia.[21]

More patients develop the neutropenia in the fall and winter seasons.[14] This seasonal variation suggests a possible association with the influenza vaccine or infection. Vesnarinone will covalently bind to activated neutrophils. Metabolism of vesnarinone by the neutrophils may produce an iminium ion and a reactive quinone imine.[22] These reactive metabolites may be responsible for the vesnarinone-induced agranulocytosis. Therefore, factors such as infection or vaccination may activate neutrophils, increase the number of reactive metabolites, and induce agranulocytosis.

3. Potential Strategies to Prevent Adverse Effects

There are several strategies that may be employed in order to minimise vesnarinone-related complications. The recently reported Multicenter Automatic Defibrillator Implantation Trial II (MADIT-2) data would suggest that all patients with ischaemic-related cardiomyopathies should

Table III. Summary of proposed mechanisms by which vesnarinone causes agranulocytosis[15]

Measurement (Objectives)	Researchers (Institution)	Results
Effects on neutrophils To investigate the effect on neutrophils	Sasada (Kyoto Univ.)	Vesnarinone had no cytotoxicity on normal human neutrophils. Vesnarinone had no effects on cell functions (release of O_2^-, phagocytic activity, chemotactic activity) in normal human neutrophils.
	Okuyama (Otsuka Pharm.)	Vesnarinone had no effects on apotosis of neutrophils from 5 affected and 4 unaffected patients.
	DeCoursey (Rush Univ.)	Vesnarinone had no effects on K^+ currents (delayed rectifier voltage gated K^+, Ca^{2+}-activated K^+ and inwardly rectifying K^+) in normal human cells and human THP-1 cells.
Effects on bone marrow precursor cells To investigate the effect on bone marrow precursors which produce granulocytes	Yamagishi (Shiga Univ.) Hara et al.(Hyogo College Med.) Furusawa (Dokkyo Univ. School of Medicine) Toyama, K. (Tokyo Med. Univ.)	Proliferation of white blood cell precursors system was inhibited in bone marrow smear samples from 5 affected patients. Vesnarinone inhibited colony formation *in vitro*. The inhibition in normal human cells and affected patient cells was not significantly different. Vesnarinone inhibited differentiation of HL-60 via stromal cells (HAS-303).
Detection of antigranulocyte antibody	Furusawa (Dokkyo University School of Medicine)	Neither drug-dependent nor drug-independent antigranulocyte antibodies were detected in sera from 3 affected patients.
Detection of anti-drug antibody	Kudo (Otsuka Pharm.)	No antibody against vesnarinone and its metabolites was detected in the serum of 2 affected patients.
Detection of antibody against bone marrow haemopoietic progenitors	Nakahata (Shinshu Univ.)	The serum samples from 5 affected patients had no antibody that is complement-dependent or –independent.
Activity of carboxy peptidase To investigate the involvement of carboxy peptidase which inhibits complement activities in the onset of granulocytopenia.	Okada (Nagoya City Univ.)	There was no significant difference in carboxy peptidase activity between the affected and the unaffected patients Affected (n = 10): Carboxy peptidase R 26.1; Carboxy peptidase N 18.3 (mean) Unaffected (n = 10): Carboxy peptidase R 21.2; Carboxy peptidase N 17.6 (mean)
Lymphocyte stimulation test To investigate the possible involvement of activated cellular immunity in the onset of granulocytopenia.	Kitamura (Tokyo Univ.)	Lymphocytes from 17 affected and 20 unaffected patients did not respond against vesnarinone and its metabolites
Detection of auto-antibody To detect auto-antibody which is related to granulocytopenia.	Kamataki (Hokkaido Univ.)	The anti-PDI (protein disulfide isomerase) antibody, one of the auto-antibodies, was detected in all serum samples from 8 affected patients and 3 unaffected patients with the exception of one affected patient. There was no significant difference between the affected and unaffected patients.
Detection of Lewis antibody To investigate the relationship of Lewis A antibody to granulocytopenia because it was found in one patient with vesnarinone-induced granulocytopenia.	Hara (Hyogo College of Medicine)	Antibody against Lewis A and Lewis B was not detected in 4 patients with granulocytopenia.

Continued next page

Table III. (cont.)

Detection of antivirus antibody To investigate the possible involvement of the initial infection in the onset of granulocytopenia	Osato (Hokkaido Univ.)	All samples from affected and unaffected patients were positive for anti-cytomegalovirus (CMV) antibody and anti-Epstein-Barr virus (EBV) antibody. This excluded the possible involvement of initial infection by EBV and CMV. However, the average value of the EBNA-IgG titre of 56 unaffected patients (98.3, especially 123.2 in 31 patients continuing vesnarinone) was higher than that of 62 affected patients (59.4). The rheumatoid factor positive rate of the affected patients was higher than that of the unaffected patients (20/62: 32.3% and 9/56: 16.1%, respectively).
N-Acetyltransferase phenotyping To investigate the possible involvement of N-acetyltransferase, a metabolic enzyme of vesnarinone, in the onset of granulocytopenia.	Ishizaki (International Med. Center)	N-Acetyltransferase has three phenotypes: slow, intermediate or rapid. The incidence of slow acetylators in the affected patients was not particularly high, and there was no difference when compared with the normal group. Affected patients: Slow type/total 2/15 (13.3%) Unaffected patients: 0/4 (0%) Normal group: 3/48 (6.3%)
Cytochrome P450 (CYP) 2D6 phenotyping To investigate the involvement of phenotype of CYP2D6 in the onset of granulocytopenia	Kamataki (Hokkaido Univ.)	According to DNA genotyping, phenotypes of 5 affected and one unaffected patient were all extensive metabolisers of CYP2D6 oxidation. According to new DNA genotyping, the genotype of only one affected patient among 23 affected and 37 unaffected patients was found to have no difference in wild and variant hetero types.
CYP1A2 genotyping To investigate the involvement of genotype of CYP1A2 in the onset of granulocytopenia	Kinoshita (Otsuka Pharm.)	Polymorphism of 2640th base in CYP1A2 was not significantly different between 39 affected and 34 unaffected patients. Affected: G/G, 4/39 (10.3%); G/A, 14/39 (35.9%); A/A, 21/39 (53.8%) Unaffected: G/G, 5/34 (14.7%); G/A:14/34 (41.7%); A/A, 15/34 (44.1%)
Plasma concentrations of vesnarinone and its metabolites To investigate the relationship of the concentrations of vesnarinone and its metabolites with granulocytopenia	Sasabe (Otsuka Pharm.)	Plasma concentrations of vesnarinone and its metabolites (OPC-18692, OPC-8230, OPC-18136, OPC-8931, OPC-8677, OPC-18137, OPC-8982) were not significantly different between 3 patients at the onset of granulocytopenia and 24 unaffected patients.
Human leucocyte antigen (HLA) typing To investigate the relationship of HLA with granulocytopenia, because it was reported that patients with clozapine-induced granulocytopenia had HLA antigens.	Sasazuki (Kyushu Univ.)	There was a significant difference in the incidence of HLA-A2 (affected vs unaffected; 57.4% vs 33.3%,), Cw7 (29.8% vs 12.3%), DRB1-1501 (27.5% vs 8.5%), DQA1-0501 (32.5% vs 15.1%) and DQB1-0602 (27.5% vs 7.5%) between 47 affected and 57 unaffected patients, respectively.
Leucocyte surface markers and sugar chain antigens	Matsuki (Otsuka Pharm.)	There was no difference in positive rates for CD markers (CD2, CD3, CD4, CD8, CD11b, CD19, CD24, CD56, CD45RA, HLA-DR, CD13, CD14, CD33, CD34) and sugar chain antigens (FH-2, FH-6, SNH-3, AH-6, TKH-2) between 15 affected and 4 unaffected patients.
Neutrophil responses To examine the effect of neutrophil chemotactic lymphokine (NCL)-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) on the chemotactic response and CD11b expression of neutrophils from affected and unaffected patients	Hirashima (Kumamoto Univ.)	The incidence of lower chemotactic indexes (CI) to NCL-4 and GM-CSF was higher in the affected patients, and the incidence of lower percentage up-regulation of CD11b expression on neutrophils was also higher in the affected patients. Affected: Lower CI NCL 6/21 (76.2%); Lower CI GM 8/10 (80.0%); Lower CD11b expression NCL 7/10 (70.0%); Lower CD11b expression GM 8/10(80.0%) Unaffected: Lower CI NCL 12/48 (25.0%); Lower CI GM 19/33 (57.6%); Lower CD11b expression NCL 9/33 (27.3%); Lower CD11b expression GM 12/33 (36.4%)

Continued next page

Table III. (contd)

Measurement (Objectives)	Researchers (Institution)	Results
Blood cytokine concentration To compare cytokine levels between affected and unaffected patients because it was reported that patients with heart failure had high levels of cytokines and there are various cytokines affecting the haemopoietic system.	Omoto (Otsuka Pharm.)	IL-1α, IL-1β,IL-2, IL-3, IL-6, TNF-α,TNF-β, GM-C SF, G-CSF, M-CSF, IFN-α, IFN-γ and IL-1α/Ab were measured in 32 affected and 55 unaffected patients. The incidence of high interleukin-6 was lower in the affected patients (1/33, 3.0%) than unaffected patients (9/43, 20.9%).

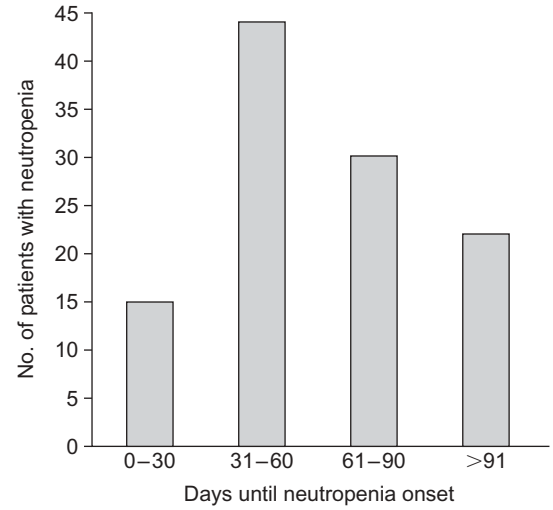

Fig. 1. Time-dependent course of vesnarinone-induced neutropenia. This graph represents the combined Japanese/US/European cases of vesnarinone-related neutropenia. The majority of patients developed neutropenia between 30 and 90 days after first-time exposure; none developed neutropenia after 26 weeks of exposure.[13,14]

have an ICD implanted.[11] The ICD would hopefully address any drug-induced fatal arrhythmias. For patients with non-ischaemic cardiomyopathies, close attention to the cardiac rhythm through routine surveillance (Holter monitoring) is mandatory. Warning arrhythmias (frequent PVCs or nonsustained ventricular tachycardia) or symptoms such as near-syncope/syncope would then warrant electrophysiological evaluation.

In-vitro cytokine testing of whole blood with regard to the effects of vesnarinone may predict which patients are susceptible to vesnarinone-induced neutropenia.[18] Additionally, there has been great interest in screening for single nucleotide polymorphisms (SNP), which may be associated with a drug response or adverse reaction. This SNP 'fingerprint' can then be used to calculate an individual's drug risk.[23] Until a better method of identifying patients susceptible to vesnarinone-induced neutropenia is detected, all patients should undergo weekly surveys of granu-

locyte count for the first 16 weeks of exposure. If the absolute granulocyte count falls $< 2000/mm^3$, administration of vesnarinone should be discontinued, and weekly granulocyte counts continued. If the absolute granulocyte count falls to $< 1000/mm^3$, the patient should be hospitalised for close observation, prophylactic antibiotic therapy, and possible G-CSF therapy.[13,14]

4. Conclusion

Vesnarinone improves the haemodynamics and quality of life in patients with CHF; however, it is associated with the adverse effects of increased sudden cardiac death and neutropenia. These adverse effects have limited the application of vesnarinone to the general population but perhaps with continued research into vesnarinone-induced neutropenia and advances in arrhythmia management, the risk/benefit ratio of vesnarinone may become favourable. For now, the use of vesnarinone should be limited to CHF patients who have exhibited a poor response to other cardiac medications and devices. These patients should be closely monitored for both cardiac and non-cardiac adverse effects.

Acknowledgements

The author has provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. OPC-8212 Multicenter Research Group. A placebo-controlled, randomized, double-blind study of OPC-8212 in patients with mild chronic heart failure. Cardiovasc Drugs Ther 1990; 4: 419-26
2. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone Study Group. N Engl J Med 1993; 329: 149-55
3. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. N Engl J Med 1998; 339: 1810-6
4. Wandel C, Lang CC, Cowart DC, et al. Effect of CYP3A inhibition on vesnarinone metabolism in humans. Clin Pharmol Ther 1998; 63: 506-11
5. Kitakaze M, Fong M, Yoshitake M, et al. Vesnarinone inhibits adenosine uptake in endothelial cells, smooth muscle cells and myocytes, and mediates cytoprotection. J Mol Cell Cardiol 1997; 29: 3413-7
6. Kitakaze M, Minamino T, Funaya H, et al. Vesnarinone limits infarct size via adenosine-dependent mechanisms in the canine heart. Circulation 1997; 95: 2108-14
7. Toyama J, Kamiya K, Cheng J, et al. Vesnarinone prolongs action potential duration without reverse frequency dependence in rabbit ventricular muscle by blocking the delayed rectifier K+ current. Circulation 1997; 96: 3696-703
8. Feldman AM, Baughman KL, Lee WK, et al. Usefulness of OPC-8212, a quinolinone derivative, for chronic congestive heart failure in patients with ischemic heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1991; 68: 1203- 10
9. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. Lancet 1990; 336: 1-6
10. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991; 325: 1468-75
11. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-83
12. Matsuyama Y, Ohashi Y, Uchino H, et al. Vesnarinone-induced WBC disorders in Japan. Pharmacoepidemiol-Drug Saf 1996; 5: 87-93
13. Furusawa S, Ohashi Y, Asanoi H. Vesnarinone-induced granulocytopenia: incidence in Japan and recommendations for safety. J Clin Pharmacol 1996; 36: 477-81
14. Bertolet B, White BG, Pepine CJ. Neutropenia occurring during treatment with vesnarinone (OPC-8212). Am J Cardiol 1994; 74: 968-70
15. Data on file. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd., 1996
16. Aizawa S, Nakano M, Yaguchi M, et al. Possible involvement of bone marrow stromal cells in agranulocytosis caused by vesnarinone treatment. Acta Haematol 1997; 98: 140-6
17. Nabeshima R, Aizawa S, Nakano M, et al. Effects of vesnarinone on the bone marrow stromal cell-dependent proliferation and differentiation of HL60 cells in vitro. Exp Hematol 1997; 25: 509-15
18. Busch FW, Tillmann A, Becker EW, et al. The inhibitory effects of a positive inotropic quinolinone derivative, 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone (OPC-8212), on bone-marrow progenitor cells and peripheral lymphocytes. Eur J Clin Pharmacol 1992; 42: 629-33
19. Matsumori A, Shioi T, Yamada T, et al. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. Circulation 1994; 89: 955-8
20. Kondo T, Suzuki Y, Kitano T, et al. Vesnarinone causes oxidative damage by inhibiting catalase function through ceramide action in myeloid cell apoptosis. Mol Pharmacol 2002; 61: 620-7
21. Nara N, Kurokawa H, Tohda S, et al. Effect of vesnarinone,

a quinolinone derivative, on the growth of leukemic blasts in acute myelogenous leukemia. Exp Hematol 1997; 25: 199–204
22. Uetrecht JP, Zahid N, Whitfield D. Metabolism of vesnarinone by activated neutrophils: implications for vesnarinone-induced agranulocytosis. J Pharmacol Exp Ther 1994; 270: 865–72
23. Guzey C, Spigset O. Genotyping of drug targets: a method to predict adverse drug reactions? Drug Saf 2002; 25: 552-60

Correspondence and offprints: Dr *Barry D. Bertolet*, Box 2519, Tupelo, MS 38803, USA.
E-mail: bbertolet@nmhs.net