

BRIEF REPORT: TREATMENT OF SEVERE COLCHICINE OVERDOSE WITH COLCHICINE-SPECIFIC Fab FRAGMENTS

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THE use of colchicine is limited by its toxicity,¹ and colchicine overdose is associated with a high mortality rate. Patients with early hemodynamic collapse due to colchicine overdose have particularly poor prognoses,^{2,3} and there has been no effective treatment for this complication of severe colchicine intoxication.⁴

Colchicine binds reversibly to tubulin,⁵ and colchicine-specific antibodies have been shown to restore the activity of tubulin *in vitro*.^{6,7} Colchicine-specific active immunization in rabbits and passive immunization in mice with substoichiometric doses of goat colchicine-specific antibodies and their Fab fragments have been shown to prevent or reverse acute colchicine poisoning.⁸⁻¹¹ These findings suggested that colchicine-specific Fab fragments could be of value in the treatment of life-threatening colchicine poisoning, such as is true of digoxin-specific Fab fragments in digitalis poisoning.¹² We here describe the successful use of this treatment in a woman who had ingested 60 mg of colchicine in a suicide attempt.

CASE REPORT

A 25-year-old woman called for medical assistance, reporting severe pains over the entire body, with predominant gastrointestinal symptoms, 24 hours after ingesting 60 tablets of Colchimax (Houdé, Puteaux, France) in a suicide attempt; these contained a total of 60 mg of colchicine (0.96 mg per kilogram of body weight), 900 mg of phenobarbital, and 750 mg of opium extract. Physical examination at the scene revealed a heart rate of 110 beats per minute and an unrecordable blood pressure. The patient was given 500 ml of colloid, and dobutamine was infused at a rate of 10 μg per kilogram per minute.

When the patient was admitted to the hospital, 27 hours after ingesting the tablets, her systolic blood pressure was 90 mm Hg, and the heart rate was 115 beats per minute. Pertinent laboratory values included the following: serum creatinine, 140 μmol per liter; prothrombin time, 26 percent of the control value; white-cell count, 69,300 per cubic millimeter; and platelet count, 268,000 per cubic millimeter. Arterial-blood gas values, measured with the patient breathing 3 liters of oxygen per minute, were as follows: pH, 7.38; partial pressure of carbon dioxide, 28.4 mm Hg; and partial pressure of oxygen, 85.5 mm Hg. Gastric lavage was performed, and activated charcoal was administered orally.

The patient was transferred to our intensive care unit 36 hours after the ingestion. Her vital signs while she was receiving dobutamine were as follows: blood pressure, 110/80 mm Hg; heart rate, 110 beats per minute; and respiratory rate, 60 breaths per minute. Over the

next three hours her temperature rose from 37.8 to 38.8°C. Her prothrombin time was 14 percent of the control value, a chest film showed pulmonary edema, and toxicologic screening revealed a plasma phenobarbital level of 60 μmol per liter and the presence of opiates in the urine.

The patient's hemodynamic status deteriorated over the next several hours despite therapy with dobutamine. Right-heart catheterization (Table 1) was performed three hours after admission, by which time the patient had received 4400 ml of crystalloid and 1100 ml of colloid. Her systolic arterial pressure subsequently declined to 65 mm Hg despite increases in the dose of dobutamine to 16 and then to 24 μg per kilogram per minute. No further hemodynamic studies could be performed because the patient became extremely restless. Her total output of urine during the first four hours in our intensive care unit was 20 ml. In view of her deteriorating condition, goat colchicine-specific Fab fragments were administered intravenously 40 hours after the drug overdose.

Within 30 minutes after the start of the Fab infusion, the systolic arterial pressure rose to 82 mm Hg, with concomitant marked improvement in all hemodynamic measurements (Table 1). During the six-hour infusion of the maintenance dose of colchicine-specific Fab, fluid replacement (with 1150 ml of colloid and 1600 ml of crystalloid) was undertaken, despite clinical signs of pulmonary edema, because the right- and left-sided filling pressures remained low. At the end of this time, the patient's temperature was normal (37.1°C). Spontaneous nonglycosuric diuresis commenced in the absence of diuretic therapy, with a mean urine output of 112 ml per hour during the 24 hours after the Fab infusion. The patient's restlessness subsided.

Although norepinephrine was used transiently in response to arterial vasodilatation, all catecholamines except low-dose dopamine were withdrawn by 27 hours after the end of the Fab infusion. Furosemide treatment was begun 44 hours after the end of the infusion, and the pulmonary edema resolved within three days after the infusion ended.

Blood cultures, including two sets of samples drawn as late as four hours after the Fab infusion, were negative at first, but 14 hours after the infusion, methicillin-sensitive *Staphylococcus aureus* was isolated and treated easily with antibiotics.

The patient's prothrombin time rose progressively, although bone marrow suppression occurred on day 4 after the ingestion, with the lowest white-cell count (1100 per cubic millimeter) occurring on day 5. Symmetric lower-limb polyneuropathy and total hair loss both occurred during the second week and eventually resolved. The patient was discharged from the intensive care unit on day 10 and from the hospital on day 25. At follow-up nine months later, she was free of sequelae.

METHODS

Preparation of Colchicine-Specific Fab Fragments

Colchicine-specific Fab fragments were prepared from the antiserum of goats immunized with a conjugate of colchicine and serum albumin as described elsewhere.¹¹ The affinity of the Fab fragments was $2 \times 10^{10} \text{ M}^{-1}$. No separation of colchicine-specific Fab fragments from other Fab fragments on the basis of immunologic affinity was performed. The percentage of colchicine-specific Fab fragments in the final preparation was 7.5 percent.

Treatment of the Patient with Colchicine-Specific Fab Fragments

A total of 6.4 g of Fab fragments (both colchicine-specific and non-specific) was reconstituted to an isotonic concentration with sterile distilled water and given in infusion to the patient through the fourth lumen of a Swan-Ganz catheter. Thus, the total amount of colchicine-specific Fab fragments equaled 480 mg. Half the dose (240 mg) was administered over a one-hour period, whereas the remaining 240 mg was infused over the ensuing six hours. A total volume of 160 ml of fluid was given as part of the Fab infusion.

The total concentration of colchicine in urine and plasma was determined by radioimmunoassay according to a modification of a method described elsewhere.¹³ Before the dosing of Fab fragments,

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Supported in part by a grant from Pasteur-Mérieux Sérums et Vaccins.

total plasma and urine colchicine was assayed directly. After the Fab infusion, the total colchicine concentration was measured according to the method of Smith et al.¹⁴ as adapted for use with colchicine.¹⁵ Unbound colchicine in urine and plasma was measured by radioimmunoassay after ultrafiltration.¹⁵

Antibodies to goat Fab fragments were detected by a radioimmunoassay on the basis of the binding of goat Fab fragments labeled with iodine-125 to the patient's serum.¹⁶

Data on the colchicine concentration over time were analyzed by model-independent analysis.¹⁷ The elimination rate constant, elimination half-life, and area under the curve of the colchicine concentration over time were calculated in standard fashion, as were the rate of urinary excretion and the renal clearance of colchicine.

Hemodynamic Studies

A four-lumen Swan-Ganz catheter (Baxter Edwards, Maurepas, France) inserted into the right jugular vein and a femoral arterial cannula were both connected to transducers (Transpac II, Abbott, Rungis, France) that were referenced to zero at the level of the mid-chest with the patient in the supine position. Hemodynamic measurements were obtained in the standard fashion.¹⁸

The study was approved by the ethics committee of the Assistance Publique-Hôpitaux de Paris. The patient gave written informed consent before receiving Fab therapy.

RESULTS

When the patient was admitted to the district hospital 27 hours after the drug overdose, the plasma colchicine concentration was 24 ng per milliliter. The administration of Fab fragments increased the total plasma colchicine concentration by a factor of 6 (from 12 to 70 ng per milliliter) 10 minutes after the start of the infusion (Fig. 1). The maximal total plasma colchicine concentration (122 ng per milliliter) was observed at the end of the start of the Fab loading dose, after which it

plateaued at 100 ng per milliliter during the six hours of the maintenance infusion. The free (unbound) colchicine concentration fell from 7.5 ng per milliliter just before the infusion to undetectable levels (<0.25 ng per milliliter) by 10 minutes after the start of the infusion, and it remained undetectable throughout the infusion. After day 4, both total and free plasma colchicine concentrations declined exponentially, with half-lives of 25 and 26.6 hours, respectively.

The Fab infusion resulted in a sixfold increase in the urinary excretion of colchicine, and a total of 5.2 mg of colchicine was recovered in the patient's urine by day 13 (Fig. 1, inset). Renally excreted colchicine was 98 percent bound to Fab fragments in the first 16 hours after the start of the Fab infusion; the fraction of urinary colchicine that was not bound gradually increased to 100 percent by 35 hours after the infusion. Colchicine was undetectable in plasma 8 days after the Fab infusion and in urine 13 days after the infusion.

No antigoat Fab antibodies could be detected in the serum of the patient 15 days after the administration of Fab.

DISCUSSION

Acute colchicine poisoning is associated with a very high mortality rate, and no specific therapy has previously been available. The reversal of colchicine poisoning in laboratory animals with the use of colchicine-specific antibodies led us to use this novel approach in a patient with a life-threatening colchicine overdose.

Deaths after acute oral colchicine poisoning seldom result from bone marrow aplasia, but are due in-

Table 1. Hemodynamic Studies of the Patient Treated with Colchicine-Specific Fab Fragments.

MEASURE	TIME BEFORE OR AFTER THE START OF THE FAB INFUSION					
	-45 MIN	-15 MIN	1 HR	6.2 HR	12 HR	37 HR
Hemodynamic variables						
Temperature (°C)	38.7	38.8	37.8	37.1	37.4	38.3
Mean right atrial pressure (mm Hg)	8	6	-4	6	2	9
Mean pulmonary-artery pressure (mm Hg)	23	18	13	20	11	22
Mean pulmonary-artery-occlusion pressure (mm Hg)	11	11	1	10	3	11
Arterial pressure (mm Hg)						
Systolic	76	78	88	65	90	92
Diastolic	52	55	52	40	62	51
Mean	60	63	64	48	71	65
Heart rate (beats/min)	126	124	115	118	118	113
Cardiac index (liters/min/m ²)	2.01	2.21	5.70	4.76	4.52	4.40
Systolic index (ml/m ²)	16.0	17.8	49.6	40.3	38.3	38.9
Left ventricular stroke-work index (g/m ²)	10.6	12.5	42.5	21.0	35.6	28.8
Systemic vascular resistance index (dyn·sec·cm ⁻⁵ /m ²)	2070	2066	954	711	1227	1024
Pulmonary vascular resistance index (dyn·sec·cm ⁻⁵ /m ²)	458	256	160	168	136	200
Arterial oxygen content (ml/dl)	17.2	17.1	14.1	16.4	12.2	8.4
Arterial oxygen saturation (%)	86.2	88.7	93.4	94.3	98.9	97.3
Venous oxygen saturation (%)	31.2	39.8	64.8	61.0	67.9	47.8
Arteriovenous difference in oxygen content (ml/dl)	11.3	10.1	4.2	3.7	4.7	4.5
Oxygen delivery (ml/min/m ²)	346	378	804	781	552	370
Oxygen consumption (ml/min/m ²)	227	223	239	176	212	198
Arterial plasma lactate (mmol/liter)	5.4	ND*	4.3	3.8	2.7	2.8
Pharmacologic variables†						
Dobutamine (μg/kg/min)	8	16	24	16	8	—
Dopamine (μg/kg/min)	—	—	—	3	3	‡
Norepinephrine (mg/hr)	—	—	—	—	0.5	—

*ND denotes not done.

†Fab was administered in a one-hour infusion of 240 mg followed by a maintenance infusion of 240 mg given over a six-hour period.

‡The infusion of dopamine was stopped briefly so that hemodynamic measurements could be made without any catecholamines present.

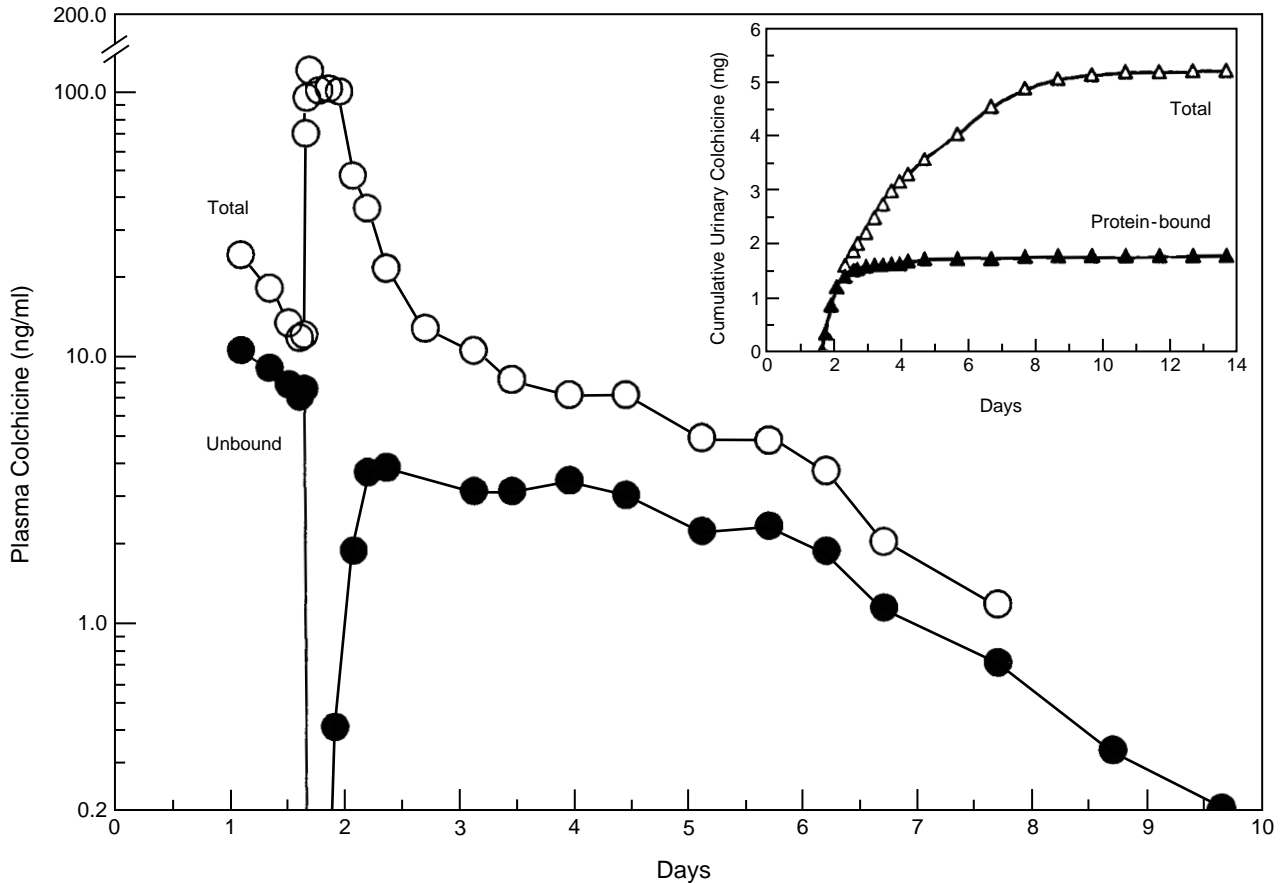


Figure 1. Concentrations of Colchicine in the Plasma and Urine of the Study Patient.

The colchicine overdose occurred on day 0, and the infusion of colchicine-specific Fab fragments began on day 1.66. For plasma colchicine, concentrations of total and unbound colchicine are shown. The inset shows the cumulative urinary excretion of total and protein-bound colchicine.

stead to hemodynamic collapse and cardiac arrhythmia.^{2,4,19-26} The mechanism of hemodynamic failure is uncertain³ but may be related to binding of the drug to microtubules in myocardial cells²⁷⁻³⁰ that play a part in various functions of heart cells.²⁷⁻³⁴ Colchicine has also been shown to impair intrinsic myocardial contractility markedly in adult rats.³⁵

We chose to administer colchicine-specific Fab fragments to this critically ill patient for several reasons. She had multiple grave prognostic features, including the ingestion of a large estimated dose,² a high plasma colchicine concentration 27 hours after ingestion,³⁶ and the hemodynamic profile of hypotension, with decreased stroke volume and increased filling pressures.^{2,3} Most important, she had worsening shock, with concurrent pulmonary edema and early signs of decreased cerebral perfusion, despite standard intensive care. We believe this patient would almost certainly have died without treatment with colchicine-specific Fab fragments.

Before the Fab infusion, the patient's hemodynamic failure was refractory to conventional treatment. The infusion of Fab fragments was temporally associated with a dramatic improvement in her clinical and hemo-

dynamic status, including a doubling of cardiac output with a beneficial decrease in preload, without the use of diuretics. Although spontaneous clearance of opiates and barbiturates could conceivably have contributed in a small way to this improvement, such clearance is unlikely to have been an important factor in her recovery. Similarly, cultures of her blood did not turn positive until well after the completion of the Fab infusion, by which time the patient's condition had already improved substantially, such that support with catecholamines was no longer required.

The administration of Fab fragments markedly altered the disposition of colchicine in this patient in a manner consistent with that described previously with regard to digoxin-specific Fab fragments in humans^{14,37} and colchicine-specific Fab fragments in rabbits and rats.^{13,15,38} The striking increase in the plasma colchicine concentration suggests that substantial amounts of the drug were removed from peripheral sites and redistributed into the extracellular space. The high affinity constant of Fab fragments for colchicine prevented the return of the drug to peripheral sites. Concentrations of protein-unbound colchicine, the toxicologically active fraction, decreased in our patient to undetectable

levels during the 7 hours of the infusion, with a subsequent partial rebound 12 hours after the start of the infusion; this also occurs during treatment with digoxin-specific antibodies.³⁷ These pharmacokinetic findings are consistent with the hypothesis that the effects of Fab fragments on the sequestration of colchicine and the redistribution of the drug from tissues into plasma could well explain our patient's clinical improvement.

Our patient had transient bone marrow suppression despite therapy with Fab fragments; clearly, this effect is not fully prevented when doses of Fab similar to that used in our patient are given hours after the ingestion and the onset of clinical toxicity. The arterial dilatation that occurred during the use of Fab was accompanied by marked improvement in all indexes of tissue perfusion and was clearly beneficial in this patient with the adult respiratory distress syndrome and decreased cardiac output; therefore, we do not believe that any adverse effects can be ascribed to the use of the Fab fragments.

We are indebted to Professor J.P. Cardinaud of the Centre Hospitalier Régional Universitaire de Bordeaux for his collaboration; to Elisabeth Cramer, M.D., for performing the hematologic studies; to Pierre Fournier and Michel Grandgeorge from Pasteur-Mérieux, who prepared the Fab fragments, for their invaluable assistance; and to Jerome Hoffman, M.D., of UCLA for his most valuable advice and criticism of this manuscript.

REFERENCES

- Roberts WN, Liang MH, Stern SH. Colchicine in acute gout: reassessment of risks and benefits. *JAMA* 1987;257:1920-2. [Erratum, *JAMA* 1987;258:2698.]
- Bismuth C, Gaultier M, Conso F. Aplasie médullaire après intoxication aiguë à la colchicine. *Nouv Presse Med* 1977;6:1625-9.
- Sauder P, Kopferschmitt J, Jaeger A, Mantz JM. Haemodynamic studies in eight cases of acute colchicine poisoning. *Hum Toxicol* 1983;2:169-73.
- Ellenhorn MJ, Barceloux DG. Colchicine overdose and colchicine-containing plant species. In: Ellenhorn MJ, Barceloux DG, eds. *Medical toxicology: diagnosis and treatment of human poisoning*. New York: Elsevier, 1988:1234-7.
- Hastie SB. Interactions of colchicine with tubulin. *Pharmacol Ther* 1991;51:377-401.
- Wolff J, Capraro HG, Bossi A, Cook GH. Colchicine binding to antibodies. *J Biol Chem* 1980;255:7144-8.
- Rouan SKE, Otterness IG, Cunningham AC, Holden HE, Rhodes CT. Reversal of colchicine-induced mitotic arrest in Chinese hamster cells with a colchicine-specific monoclonal antibody. *Am J Pathol* 1990;137:779-87.
- Scherrmann JM, Urtizberea M, Pierson P, Terrien N. The effect of colchicine-specific active immunization on colchicine toxicity and disposition in the rabbit. *Toxicology* 1989;56:213-22.
- Terrien N, Urtizberea M, Scherrmann JM. Reversal of advanced colchicine toxicity in mice with goat colchicine-specific antibodies. *Toxicol Appl Pharmacol* 1990;104:504-10.
- Urtizberea M, Sabouraud A, Cano N, Grandgeorge M, Rouzioux JM, Scherrmann JM. Reversal of murine colchicine toxicity by colchicine-specific Fab fragments. *Toxicol Lett* 1991;58:193-8.
- Sabouraud A, Urtizberea M, Grandgeorge JM, Gattel P, Makula MF, Scherrmann JM. Dose-dependent reversal of acute murine colchicine poisoning by goat colchicine-specific Fab fragments. *Toxicology* 1991;68:121-32.
- Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxications with digoxin-specific Fab antibody fragments: final report of a multicenter study. *Circulation* 1990;81:1744-52.
- Sabouraud AE, Urtizberea M, Benmoussa K, Cano NJ, Scherrmann JM. Fab-bound colchicine appears to adopt Fab fragment disposition in rats. *J Pharm Pharmacol* 1992;44:1015-9.
- Smith TW, Haber E, Yeatman L, Butler VP. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 1976;294:797-800.
- Sabouraud AE, Urtizberea M, Cano NJ, Grandgeorge M, Rouzioux J-M, Scherrmann J-M. Colchicine-specific Fab fragments alter colchicine disposition in rabbits. *J Pharmacol Exp Ther* 1992;260:1214-9.
- Thanh-Barthet CV, Urtizberea M, Sabouraud AE, Cano NJ, Scherrmann JM. Development of a sensitive radioimmunoassay for Fab fragments: application to Fab pharmacokinetics in humans. *Pharm Res* 1993;10:692-6.
- Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. Vol. 15 of *Drugs and the pharmaceutical sciences*. New York: Marcel Dekker, 1982.
- Perret C, Tagan D, Feihl F, eds. *Le cathétérisme cardiaque droit en soins intensifs*. Paris: Arnette, 1993.
- Stapczynski JS, Rothstein RJ, Gaye WA, Niemann JT. Colchicine overdose: report of two cases and review of the literature. *Ann Emerg Med* 1981;10:364-9.
- Stahl N, Weinberger A, Benjamin D, Pinkhas J. Fatal colchicine poisoning in a boy with familial Mediterranean fever. *Am J Med Sci* 1979;278:77-81.
- Favarel-Garrigues J-C, Bony D, Poisot D. Intoxications aiguës par la colchicine: a propos de 7 observations. *Concours Med* 1975;97:5183-97.
- Lambert H, Laprévote-Heully MC, Manel J, Gilgenkrantz S, Larcen A. Les intoxications aiguës par la colchicine: a propos de 22 observations. *Ann Med Nancy Est* 1981;20:891-900.
- Hobson CH, Rankin APN. A fatal colchicine overdose. *Anaesth Intensive Care* 1986;14:453-5.
- Ellwood MG, Robb GH. Self-poisoning with colchicine. *Postgrad Med J* 1971;47:129-31.
- Hill RN, Spragg RG, Wedel MK, Mosker KM. Adult respiratory distress syndrome associated with colchicine intoxication. *Ann Intern Med* 1975;83:523-4.
- Caplan YH, Orloff KGT, Thompson BC. A fatal overdose with colchicine. *J Anal Toxicol* 1980;4:153-5.
- Klein I. Colchicine stimulates the rate of contraction of heart cells in culture. *Cardiovasc Res* 1983;17:459-65.
- Nath K, Shay JW, Bollon AP. Relationship between dibutyryl cyclic AMP and microtubule organization in contracting heart muscle cells. *Proc Natl Acad Sci U S A* 1978;75:319-23.
- Limas CJ. Myocardial colchicine-binding proteins: possible relation to DNA synthesis initiation. *J Mol Cell Cardiol* 1979;11:1137-50.
- Crie JS, Ord JM, Wakeland JR, Wildenthal K. Inhibition of cardiac proteolysis by colchicine: selective effects on degradation of protein subclasses. *Biochem J* 1983;210:63-71.
- Rybicka K. Microtubules in the ventricular specialized conducting fibers of the dog heart. *J Mol Cell Cardiol* 1978;10:409-14.
- Simpson P, Savion S. Differentiation of rat myocytes in single cell cultures with and without proliferating nonmyocardial cells: cross-striations, ultrastructure, and chronotropic response to isoproterenol. *Circ Res* 1982;50:101-16.
- Rappaport L, Samuel JL. Microtubules in cardiac myocytes. *Int Rev Cytol* 1988;113:101-43.
- Lampidis TJ, Trevorrow KW, Rubin RW. Effects of colchicine on cardiac cell function indicate possible role for membrane surface tubulin. *Exp Cell Res* 1986;164:463-70.
- Mery P, Riou B, Chemla D, Lecarpentier Y. Cardiotoxicity of colchicine in the rat. *Intensive Care Med* 1994;20:119-23.
- Rochdi M, Sabouraud A, Baud FJ, Bismuth C, Scherrmann JM. Toxicokinetics of colchicine in humans: analysis of tissue, plasma and urine data in ten cases. *Hum Exp Toxicol* 1992;11:510-6.
- Schaumann W, Kaufmann B, Neubert P, Smolarz A. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986;30:527-33.
- Sabouraud A, Redureau M, Gires P, Martinet M, Scherrmann JM. Effect of colchicine-specific Fab fragments on the hepatic clearance of colchicine. *Drug Metab Dispos Biol Fate Chem* 1993;21:997-1002.