ADVERSE DRUG REACTIONS ASSOCIATED WITH THE USE OF RIBAVIRIN IN THE TREATMENT OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

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ABSTRACT

Background
Health Canada's Special Access Programme (SAP) provided access to nonmarketed formulations of ribavirin (oral and parenteral) to physicians treating patients with probable or suspect SARS from March 14, 2003 to April 26, 2003.

Objectives
To report on an active surveillance programme employed to monitor adverse drug reactions associated with the use of ribavirin in the treatment of SARS.

Methods
A series of notices were sent to hospitals requiring the submission of any and all ADRs associated with the use of ribavirin in the treatment of SARS. The ADRs were coded using ADR terminology of the World Health Organization Collaborating Centre for International Drug Monitoring (WHO-ART). Causality assessments were performed using the assessment algorithm of the WHO.

Results
The SAP authorized access to ribavirin for a total of 246 patients at hospitals in Ontario and British Columbia. A total of 126 ADR reports were received. Hypocalcemia and hypomagnesemia were the most common ADRs reported with 55 and 59 reports respectively. Hemolytic anemia was reported as an ADR in 41 patients and transfusions were reported in 12 cases. Decreased hemoglobin was reported as an ADR in 34 patients and transfusions were reported in 8 cases.

Discussion
The population of patients treated with ribavirin was known and permitted an accurate understanding of the incidence of ADRs. Health care officials are challenged to develop the capacity to ensure that the use of a drug in a novel disease is carried out in a controlled setting to maximize the integrity of data collection and patient protection.

Key Words: SARS; ribavirin; ADR surveillance; hemolytic anemia; hypocalcemia; hypomagnesemia

The emergence of severe acute respiratory syndrome (SARS) as a new communicable disease has challenged the capacity of local, national and international health authorities to manage an important health threat. Individual jurisdictions responded to the immediate public health needs of their respective populations, but the response was also characterized by unprecedented international cooperation.[1] Indeed, collaboration among authorities led to a

worldwide health alert on March 12, 2003 issued by the World Health Organization (WHO).[2] This was followed by the early development of case definitions,[3] diagnostic tests,[4,5] containment strategies[6] and treatment regimens.[7-9] Within one month of the WHO alert, laboratories reported the isolation and identification of a new virus, [10-12] the sequence of the viral genome,[13,14] and further work on more reliable diagnostic techniques [15,16] all of which constituted a platform for the development of strategies to manage and contain the disease.

The clinical management of the first SARS patients was reported by a number of jurisdictions including Hong Kong,[17-19] Singapore[20] and Canada.[21-23] Subsequent reports provided further detail on the successes and failures of various therapeutic interventions.[24-26] In Canada, the first patients were treated with a combination of antibacterial and antiviral drugs including levofloxacin, ribavirin, oseltamivir, and steroids, in conjunction with intensive and supportive care.[21] Guidelines distributed by local public health authorities within a week of the diagnosis of the first Canadian patient represented the first official guidance for treating both suspect and probable cases of SARS in Canada.[8] Experience from these early cases subsequently led to the development of Health Canada's interim recommendations for health care providers for the management of SARS.[27] These measures were consistent with recommendations at that time from clinicians treating patients in Hong Kong[28] and Singapore (personal communication), where anecdotal evidence suggested that ribavirin, steroids and convalescent sera may have been of clinical benefit.

Two formulations of ribavirin are approved for sale in Canada: oral capsules for the treatment of hepatitis C sold in combination with interferon alpha[29,30] and powder for inhalation for the treatment of respiratory syncytial virus (RSV).[31] During the SARS outbreak, the oral capsules were not available in sufficient quantities and the inhaled formulation was considered inappropriate due to the extent of respiratory compromise in many patients. Health Canada's interim recommendations therefore included the use of intravenous and oral tablet formulations of ribavirin, neither of which were approved in Canada but were made available upon request through Health Canada's Special Access Programme (see Box 1).

BOX 1:

Special Access Programme

Health Canada's Special Access Programme (SAP) provides access to nonmarketed drugs for practitioners treating patients with serious or life-threatening conditions where conventional therapies have failed, are unsuitable, or unavailable. The SAP authorizes a manufacturer to sell a drug that cannot otherwise be sold or distributed in Canada. Drugs considered for release by the SAP include pharmaceutical, biologic, and radio-pharmaceutical products.

The SAP does not authorize the use or administration of a drug - this authority falls within the practice of medicine, which in Canada is regulated at the provincial level. SAP authorization does not constitute an opinion or statement that a drug is safe, efficacious or of high quality. The SAP does not conduct a comprehensive evaluation to ensure the validity of drug information or attestations of the manufacturer respecting safety, efficacy and quality.

The regulatory authority to permit the sale of non-marketed drugs for emergency purposes is found in sections C.08.010 and C.08.011 of the *Food and Drug Regulations.* [55] Under this authority, the Health Products and Food Branch has the authority to permit the sale of a new drug to a practitioner, if the practitioner has supplied satisfactory information on the nature of the

medical emergency, the data he or she has about the drug's use, safety and efficacy, the names of the institutions where the drug is to be used, and other such data as the programme may require. In addition, the practitioner must agree to provide a report on the results of the use of the drug including information on adverse drug reactions and, on request, to account for the quantities of drug released. The first e-mail notice was distributed to hospitals on March 29, 2003 detailing the first seven reports of hemolytic anemia with the use of ribavirin for SARS treatment.

Active surveillance of ADRs was initiated on March 31, 2003 with a second e-mail notice to the hospitals. Health care professionals were made aware of the intention to actively survey ADR information and the mechanisms for reporting ADRs (see Box 2), and were provided a copy of the Health Canada ADR reporting form. The ADR reporting form includes general guidance on what to report and on how to report ADRs. Standard definitions for the ADRs were not provided. Each hospital was contacted by telephone to confirm receipt of the notice, to inquire about the knowledge of ADRs at the hospital, and to determine each centre's anticipated schedule for submitting ADR reports. Receiving reports by telephone facilitated the submission of ADR reports.

Ribavirin is a purine nucleoside analogue with documented activity against a wide variety of RNA and DNA viruses[32] and it was this spectrum of antiviral activity that led to the initial use of ribavirin for SARS. Ribavirin is also known to inhibit paramyxoviruses such as parainfluenza virus and RSV[31,33] and early reports cited a paramyxovirus as a possible causative agent of SARS.

Ribavirin is associated with a wide range of adverse drug reactions. These are detailed in drug information sources including the Canadian product monographs[29-31] and other sources of drug reference information available to health care professionals.[33] Koren *et al*[34] provided a review of the drug in the context of its use in the treatment of SARS including its adverse effects and potential reproductive toxicity.

Despite the well documented adverse effects of ribavirin, its use in the treatment of SARS involved several unique circumstances including extensive use in patients with a new viral disease and its combined use with several other drugs. In addition, the recommended doses, drawn from experience with Lassa fever[35] and other viral hemorrhagic diseases,[36] were higher than those used in the treatment of hepatitis C. Indeed, it was this unusual scenario of drug use that raised the possibility of under-reporting of adverse drug reactions and prompted Health Canada's active surveillance and assessment of adverse drug reactions.

We report here on the results of an active surveillance programme employed to monitor the use of both oral and parenteral ribavirin in the treatment of SARS patients in Canada. Central access to the drug and regulatory control over the drug afforded the opportunity to survey and analyse adverse drug reactions as they were reported to Health Canada by health care professionals from a defined cohort of patients.

We expect that our results will contribute to the continuing interpretation of anomalies identified during retrospective case reviews as clinicians assess the success of treatment interventions and the management of SARS patients in general.

METHODS

Special Access Programme and access to ribavirin

Emergency access to oral and parenteral ribavirin for the treatment of SARS was permitted through Health Canada's Special Access Programme (SAP) on a patient-by-patient basis, from March 14, 2003 to April 26, 2003. The release of ribavirin through the SAP was restricted to patients meeting the probable case definition, and

to patients meeting the close contact component of the suspect case definition in use at that time.[37]

Active surveillance methods and source of data

The first verbal notifications of adverse drug reactions (ADRs) associated with ribavirin were received on March 27 and 28, 2003. A contact list of hospitals using ribavirin during the course of the first SARS outbreak was compiled and updated on an ongoing basis as additional hospitals requested ribavirin.

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BOX 2

Reporting Adverse Reactions

Health professionals and consumers can contact Health Canada or a Regional Adverse Reaction (AR) Centre:
Tel: 866-234-2345
Fax: 866-678-6789

Manufacturers of health products should contact Health Canada directly:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address locator: 0701C
Ottawa, Ontario, K1A 0K9
Tel: 613-957-0337
Fax: 613-957-0335
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_report_e.html

Three additional e-mail notices were sent to hospitals between April 5 and April 16, 2003 to provide updated information on ADRs reported to Health Canada in that time period. Routine access to ribavirin was discontinued on April 26 and a sixth e-mail notice was sent on April 27 providing advance notice of the anticipated change to the Health Canada treatment guidelines.

On May 8, 2003 a seventh e-mail notice was sent to update hospitals on the ADRs received to date, to draw attention to the teratogenic risks of ribavirin, and to request any ADR reports not yet submitted. Each hospital was subsequently contacted by telephone to confirm that all ADRs had been reported or that none had been observed.

Data processing, WHO-ART

Adverse drug reaction reports received by Health Canada were sent to the SAP or to Health Canada Regional Adverse Reaction Centres and transferred to Health Canada's Marketed Health Products Directorate (MHPD) (see Box 3). Initial assessment of the ADR reports included an evaluation of the seriousness of the report and coding using the adverse reaction terminology of the World Health Organization Collaborating Centre for International Drug Monitoring (WHO-ART).[38] Information from the ADR reports was entered into Health Canada's Canadian Adverse Drug Reaction Information System (CADRIS) database and included: age, sex, drug names, role of each drug as assigned by the reporter of the ADR (suspected, concomitant, interacting, treatment), dose, duration of use, dates of use, date of onset of reaction(s), coding in WHO-ART terminology and outcome of the patient at the time of report.

BOX 3

Marketed Health Products Directorate

The Marketed Health Products Directorate (MHPD) is responsible for coordination of post-approval surveillance and assessment of signals and safety trends concerning all marketed health products. The MHPD conducts the following range of activities:

- monitors and collects adverse reaction and medication incident data, reviews and analyses marketed health product safety data,
- conducts risk/benefit assessments,
- communicates product related risks to health care professionals and the public,
- coordinates regulatory advertising activities,
- develops post-approval policy, and
- conducts active surveillance and drug effectiveness projects

Causality assessment

Medical and scientific evaluators performed causality assessments of case reports of adverse reactions associated with the use of ribavirin using the causality assessment algorithm of the WHO (see Box 4).[3] Causality assessments were performed by an evaluator and peer reviewed by a second evaluator. In the case of differing assessments, the evaluators reviewed the reports together and reached an agreement on the assessment. Additional evaluators were not required to resolve any disagreements.

BOX 4

WHO Causality Assessment of Suspected Adverse Reactions

Certain:
A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely:
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible:
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely:
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified:
A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/Unclassifiable:
A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

RESULTS

During the first wave of SARS in Canada, a total of 318 patients[40] were diagnosed with either probable or suspect SARS. Between March 14 and April 26, 2003, the SAP provided authorization to access oral and parenteral ribavirin for 77% of patients (n= 246; 151females, 95 males) at 26 hospitals in Ontario and British Columbia. A total of 126 ADR reports (83 females, 43 males) were received by Health Canada between March 31 and May 8, 2003 (see Table 1). Two reports involved fatal outcomes. It should be noted that a report of a fatal outcome does not establish that the ADR was a direct or contributory cause of death.

Adverse drug reactions associated with the use of ribavirin in the treatment of Severe Acute Respiratory Syndrome (SARS)

TABLE 1: Reactions described in 126 reports submitted to Health Canada, March 31, 2003 to May 8, 2003

SYSTEM ORGAN CLASS (SOC)	REACTION TERM *WHO-ART Terminology*	*NUMBER OF REACTIONS*	*% OF PATIENTS TREATED*
Metabolic and Nutritional Disorders	*Hypocalcemia*	*59*	*24.0*
	Hypomagnesemia	*55*	*22.4*
	LDH increased	*25*	*10.1*
	Creatine phosphokinase increased	*12*	*4.9*
	Hypokalemia	*5*	*2.0*
	Hypophosphatemia	*5*	*2.0*
	BUN increased	*2*	*0.8*
Red Blood Cell Disorders	*Hemolytic anemia*	*41*	*16.7*
	Decreased hemoglobin	*34*	*13.8*
	Reticulocytosis	*4*	*1.6*
Liver and Biliary System Disorders	*Bilirubinaemia*	*37*	*15.0*
	SGOT (AST) increased	*32*	*13.0*
	SGPT (ALT) increased	*24*	*9.8*
	Hepatitis	*4*	*1.6*
	Alkaline phosphatase increased	*3*	*1.2*
Gastrointestinal System Disorders	*Nausea*	*10*	*4.1*
	Vomiting	*4*	*1.6*
	Dysphagia	*4*	*1.6*
	Stomatitis	*3*	*1.2*
	Dyspepsia	*2*	*0.8*
White Cell and Reticulo-endothelial Disorders	*Lymphopenia*	*16*	*6.5*
	Leucopenia	*6*	*2.4*

Adverse drug reactions associated with the use of ribavirin in the treatment of Severe Acute Respiratory Syndrome (SARS)

SYSTEM ORGAN CLASS (SOC)	REACTION TERM *WHO-ART Terminology*	*NUMBER OF REACTIONS*	*% OF PATIENTS TREATED*
Reactions reported once only	*Abdomen enlarged* *Agitation* *Amylase increased* *Confusion*	*1 each*	*0.8% each*

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

ADR case reports were evaluated using the following variables: sex, age, duration of exposure to ribavirin, day of detection of the adverse reaction (day 1 = first day of ribavirin therapy), and causality. Some reports were incomplete and as a result the "n" for a specific variable (i.e., duration of exposure) may not equal the total number of reports received. Data was not separated by exposure to oral versus intravenous ribavirin due to incomplete timeline data in some reports and the high occurrence of exposure to both products.

Hypocalcemia and hypomagnesemia

The most common ADRs reported with the use of ribavirin during the surveillance period were hypocalcemia and hypomagnesemia. Hypocalcemia was reported as an ADR in 55 patients (22.4% of patients treated). Hypomagnesemia was reported as an ADR in 59 patients (24% of patients treated). Most often they were both reported in the same patient (39 patients). The average patient age was 48 years (n = 75, range 17–99 years; 25 males, 50 females). The duration of ribavirin therapy was reported as ranging from 3–10 days, with a mean duration of 7 days (n = 72).

In the reports of hypocalcemia, the average time to detection was 2.7 days (range 1–10 days, n = 38). In 14 cases the detection of hypocalcemia was reported to be the day of initiation of ribavirin therapy, and it is unclear if the condition was present prior to therapy. Tetany was reported in 3 patients with hypocalcemia.

In the reports of hypomagnesemia, the average time to detection was 2.9 days (range 1–6 days, n = 40). In 7 cases the detection of hypomagnesemia was reported to be the day of initiation of ribavirin therapy, and it is unclear if the abnormality was present prior to initiation of ribavirin therapy.

In 51 reports the reporter indicated that the patient was treated for the electrolyte abnormality (ies). Causality was assessed as "possible" in all but 8 cases, where causality was assessed as "unclassified" because of insufficient information.

Hemolytic anemia

Hemolytic anemia was reported as an ADR in 41 patients (14 males, 27 females; 16.7% of patients treated). The average patient age was 41 years (range 17–99 years). The duration of ribavirin therapy was reported as ranging from 3–12 days, with a mean duration of 7.4 days (n = 39). The average time to detection of hemolytic anemia was 6.5 days (range 2–14 days, n = 35). Hemoglobin concentration fell by an average of 39 g/L (range 10–82 g/L, n = 35), with only two reports of drops <20 g/L. Transfusions were reported in 12 cases (29% of those with hemolytic anemia); patients who were treated with transfusions had an average age of 52 years and 7 were female. Causality was assessed as "probable" in 4 cases and "possible" in 37 cases.

Decreased haemoglobin

Decreased hemoglobin was reported as an ADR in 34 patients (10 males, 24 females; 13.8% of

patients treated). The average patient age was 52 years (range 22–88 years). The duration of ribavirin therapy was reported as ranging from 4–21 days, with a mean duration of 8.3 days (n = 34). The average time to detection of decreased hemoglobin concentration was 4.1 days (range 2–10 days). Hemoglobin concentration fell by an average of 33 g/L (range 7–58 g/L, n = 23), with only two reports of drops <20 g/L. Transfusions were reported in 8 cases (23.5% of those with decreased hemoglobin; 2 males and 6 females); patients who were treated with transfusions had an average age of 76 years (range 64–88 years). Causality was assessed as "probable" in 6 cases and "possible" in 28 cases.

Other reactions

A total of 23 reactions were reported only once: abdomen enlarged, agitation, amylase increased, confusion, convulsions, C-reactive protein positive, creatinine blood increased, creatinine clearance decreased, electrolyte abnormality, fever, hallucination, headache, hematuria, hyponatremia, leukocytosis, metallic taste, parasthesia, pharyngitis, pruritus, rash, restless legs, tongue protrusion, urine discolouration.

DISCUSSION

Monitoring the adverse effects of drugs in the marketplace is a challenge for health care professionals, regulators and manufacturers alike. The most commonly employed monitoring systems are those that rely on voluntary reporting of adverse reactions by health care professionals. While there are advantages to passive surveillance systems, it is widely recognized that under reporting and the lack of a denominator of drug use limits the ability to draw meaningful interpretations from spontaneously reported reactions.[41] By comparison, active surveillance can estimate the incidence of adverse reactions in a given population with greater accuracy.[42] This information is useful to clinicians, manufacturers and regulators who collectively monitor the safety and effectiveness of drugs in 'real world' settings as well as to consumers by enabling informed decision-making about therapeutic choices.

Health Canada's direct control over access to ribavirin for the treatment of SARS afforded the opportunity to actively monitor safety experience by tracking the release of drug supply on a patient-by-patient basis, establishing direct contact with hospitals, and requiring submission of adverse drug reactions as suspected by health care professionals responsible for the care of SARS patients. Other published reports have described treatment experiences in one or more centers and it is important to note that these data are subsets of our total Canadian data set. Our report therefore represents a unique contribution and understanding of the incidence of ADRs and the significant and serious safety concerns resulting from the use of high doses of ribavirin to treat SARS in Canada. These reactions, attributed to the use of the drug, encompass the spectrum of serious to nonserious and from expected to unexpected.[43]

Hypocalcemia and hypomagnesemia were the most common ADRs reported and led to calcium and magnesium supplementation for most patients. The occurrence of hypocalcemia and hypomagnesemia in SARS patients treated with ribavirin was an unexpected ADR. As a result, calcium and magnesium testing was not always performed or was not performed routinely, and therefore it is not possible to know the day of onset of the condition and whether it occurred prior to the initiation of ribavirin treatment. Instead, we determined the first day of ribavirin treatment to be day 1 for the purposes of our analysis. In 24% of the hypocalcemia reports and 13% of the hypomagnesemia reports, the abnormality was detected on the day of initiation of ribavirin therapy. It is therefore possible that these conditions were pre-existing and that either or both of these abnormalities would have evolved over the natural course of the disease, or that ribavirin exacerbated the abnormalities.

Hypocalcemia has been reported in patients treated with ribavirin (1000–1200 mg daily) as part of combination therapy for chronic hepatitis C.[44] Data published by Booth *et al*[22] reported hypocalcemia in 60% of 144 patients with a diagnosis of suspected or probable SARS; many of the patients described in that study are also included in our analysis.

Hemolytic anemia is a well-known adverse drug reaction associated with ribavirin therapy. Clinical trials have shown that hemolytic anemia develops in 10 to 14% of patients treated with ribavirin + interferon.[29,30] During the surveillance period, Health Canada received 41 reports (16.7% of patients treated) of hemolytic anemia and an additional 34 reports (13.8% of patients treated) of decreased hemoglobin. It is possible that some events reported as decreased hemoglobin were actually hemolytic anemia, however the reports did not indicate or show evidence of hemolysis. We note that hemoglobin disturbances were collectively reported in 75 patients, i.e. 30.5% of patients treated. Of the 75 patients with reported hemoglobin disturbances, 26.7% (20 patients) were reported as receiving transfusions, an indication of the seriousness of the anemia and its compromising effect on these patients. The higher incidence of hemoglobin disturbances in SARS patients treated with ribavirin compared with those treated for hepatitis C may be associated with the high doses that were initially used to treat SARS. Most cases of hemolytic anemia and decreased hemoglobin were reported as "possible", rather than "probable" ADRs. However, most reports were received while patients were still being treated and there was insufficient time to determine if dechallenge was successful, which could possibly change a "possible" assessment to "probable".

Given that treatment protocols employed by various jurisdictions were for the most part uncontrolled, the incidence of individual reactions, including hemoglobin disturbances, is widely variable. We note that our results (n=246, 31%) sit at the lower end of experience compared with other published results: Booth et al.[22] n=126, 49%; Knowles *et al*[45] n= 110, 61%; Sung *et al*[25] n=138, 33%; Ho *et al*[26] n=72, 24%; Leong *et al*[46] n=97, 73%. Variables such as dosing, dosage form, number of patients, patient status, intercurrent illness, under-reporting, patient management practices, and characterization of hemoglobin disturbances may have individually or collectively contributed to these discrepancies.

Despite the advantages of active surveillance over passive surveillance our study is limited on a number of fronts. As officials struggled to manage the disease, it is possible that ADRs were under-reported particularly with the use of ribavirin early in the outbreak. Conversely, active surveillance can stimulate reporting beyond that normally obtained with a spontaneous reporting system including reports not causally linked to the product. We did not provide standard definitions for the ADRs but rather categorized them on the basis of diagnoses made at each institution, many of whom did employ institution specific definitions.[22,45]

Our data is also limited in determining onset of some reactions because the ADR reports were not always complete and not all patients were routinely tested for all parameters every day. For instance, the date of apparent detection is a crude estimate of onset for hypocalcemia and hypomagnesemia. However, it may be a better estimate of onset of hemolytic anemia and decreased hemoglobin, as these are expected adverse drug reactions previously known to be associated with ribavirin[29,30] and patients may have been more frequently monitored for such events. We note that the detection of hemolytic anemia in the group of SARS patients was 6.5 days, which is slightly earlier than reported in clinical trials where the onset of hemolytic anemia with ribavirin therapy is reported to be 1 to 4 weeks after starting therapy.[29,30]

Other frequently reported adverse drug reactions were increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH).

Increased transaminase levels are not known adverse drug reactions associated with ribavirin, but have been seen with levofloxacin therapy, which most patients were receiving concurrently with ribavirin. Booth *et al*[22] reported an increased LDH as a finding in SARS patients and increased transaminases were noted in the patients reported by Peiris et al.[47] and Wu.[48]

Our study may have been helped by comparing various clinical parameters of the 246 patients treated with ribavirin with the 72 patients that were not treated with ribavirin. However, the SAP did not have the regulatory authority to solicit information beyond treatment experience with ribavirin. We note with interest the observations by Loutfy *et al*[49] that mean hemoglobin, calcium, total bilirubin, alkaline phosphatase, aspartate aminotransferase and creatinine values were all within normal ranges for SARS patients treated with interferon and corticosteroids.

The current summary focuses on ADR reports received during or immediately following treatment with ribavirin. The ADR reports received during the surveillance period suggest short-term toxicities only, and there is no indication of medium- or long-term sequelae associated with ribavirin use. However, the teratogenic potential of ribavirin, as a nucleoside analogue, is worthy of note. As discussed by Koren *et al*[34] rodent studies have shown that ribavirin is teratogenic at relatively low doses yet this effect is not seen in non-human primate studies at doses up to 60-120 mg/kg. An industry-based registry from Schering Plough Inc. did not indicate a higher than expected teratogenic rate among several hundred pregnant patients with hepatitis C who received oral ribavirin during pregnancy.[34] However, the risks remain unquantified.

The goal of Health Canada's active surveillance of ribavirin was to gather and disseminate drug safety information to health care professionals at all centers during the outbreak. The programme also prompted clinicians to be on alert for both anticipated reactions and other anomalies that may have represented new safety signals. Indeed, concern about the adverse drug reactions being reported with the use of ribavirin and questions about its efficacy led health care professionals in the Greater Toronto Area to lower the dosage of ribavirin being administered to SARS patients. Soon after, these reports of serious and unexpected adverse drug reactions, a review of the clinical data from Toronto [later published by Booth *et al*[22]] and negative results from in vitro testing with ribavirin against SARS related coronavirus led an expert working group advising Health Canada to exclude ribavirin from the treatment guidelines for SARS.[50]

We acknowledge the extraordinary pressure that clinicians faced in the early response to SARS as they confronted and cared for sick patients - some of who were colleagues - without a cure or the confidence that their efforts would be of benefit. We also acknowledge that compassionate access to drugs through Health Canada's Special Access Programme represented one of the only options for physicians to obtain access to unapproved drugs identified as possible treatment options. The urge to treat was both understandable and at the same time problematic; understandable, because clinicians are expected to solve problems and use all available means in the best interests of patients; problematic, because the use of a known drug for a new indication is best captured within the context of clinical research where hypotheses can be tested and where there is opportunity to generate meaningful and interpretable data.

The shortcomings of employing ribavirin in a compassionate use setting are now obvious.[46,51-53] Many reports of treatment experience with SARS describe serious limitations with respect to methodology, quality of data and the interpretability of data.[22,23,28,34] These reports therefore are of little value in determining the risks and benefits of ribavirin treatment and are limited in their ability to generate meaningful evidence to support or modify treatment regimens in real time.[42] Reports of serious adverse drug

reactions combined with the uncertainty regarding the effect of ribavirin on the clinical course of the syndrome underscores that only well designed randomized controlled clinical trials can determine how well drugs are tolerated and ultimately how safe and efficacious a drug is in a given clinical circumstance. For example, trials could be employed to resolve treatment controversies such as the use of traditional Chinese medicine and suggestions that combination treatment contributed to a lower case fatality rate in SARS patients in China.[54]

The efforts of officials to share information quickly have lead to a growing understanding of the natural history of SARS within a very short period of time. Indeed within a year of the WHO alert, hundreds of articles have been published on all aspects of the disease. It is now known that SARS is a highly infectious viral disease with variable presentation and course, and a relatively high mortality rate. While there is much effort aimed at responding to the disease a complete understanding will remain a long-term goal. We therefore acknowledge that our data and data from other centres should be reviewed to distinguish between what is suspected as an ADR and what may turn out to be a marker for the disease. We note the observations that ribavirin may have unmasked or accentuated hypomagnesemia as a disease related effect[45] and that coronavirus causing SARS might induce liver damage.[48]

The world will undoubtedly face new diseases beyond SARS in the future. As we search for treatment options and prepare for future new diseases, the challenge for clinicians, regulators and manufacturers will be to develop the capacity to respond rapidly to a novel disease by proposing treatment hypotheses a priori early in an epidemic and to anticipate the regulatory and institutional logistics in advance.

The efforts of a number of working groups coordinated by the WHO,[55] and the reflective and considered commentary from Toronto area clinicians[51] have advanced discussion on the need for prospective clinical research to be employed in health emergencies. Amongst many considerations, we recommend that interim analysis of safety and efficacy be incorporated into any trial design to support real time decision-making regarding treatment continuation. Experience could be drawn from other aspects of public health response planning and applied to the rapid design, approval and implementation of clinical trials, which will maximize the integrity of data collection and patient protection.

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