Virginiamycin Risk Assessment

Comments on the Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* attributable to the Use of Streptogramins in Animals *"Virginiamycin Risk Assessment"*.
Released by FDA Center for Veterinary Medicine. Draft for Comment, 23-Nov-04

Comments by;

Dr Peter Collignon, Infectious Diseases Physician and Microbiologist
Director Infectious Diseases Unit and Microbiology Department, The Canberra Hospital.
Professor, Canberra Clinical School. Australian National University and the University of Sydney.

The Canberra Hospital, Garran, ACT. Australia.
PO Box 11, Woden. ACT. 2607. Australia.
fax 61 2 6281 0349, phone 61 2 6244 2105, email peter.collignon@act.gov.au

January 24 2005.

Introduction

I believe the current FDA risk assessment significantly underestimates the numbers of people in the U.S. that currently have an adverse outcome per year with bacteraemia and other serious infections caused by *Enterococcus faecium*. However even figures based on these current under-estimates still mean that when the most likely scenario is utilized from the recently published "virginiamycin risk assessment", that each year in the U.S. many people with septicemia caused by *Enterococcus faecium* (between 20 to 120 people) will have a poor outcome as the result of the use of virginiamycin in food animals.

Current estimates of people with serious adverse outcomes due to virginiamycin use in animals in the US (FDA risk assessment).

If we accept the assessment's 10% scenario model (i.e. that only 10% of streptogramin resistance seen in people is due to virginiamycin use in animals), then for the U.S. population the estimated risk of a poor outcome is 0.7 to 4 per 100 million per year. This may not seem to be a very high risk but for those individuals (and their families) this will have a fairly devastating effect, especially if death results. In the U.S. (300 million) this would translate to about 7 people per year (range 2 -12 people) and results from the use of virginiamycin in food animals.

	Rate	Affected Americans Annually (Range)	Affected Americans (Median estimated)
10% scenario	.7 to 4 per 100 million	2 - 12	7
100% attributable model		20 to 120	70

However, I believe that it is more realistic to look at their "100% attributable model" (as discussed in the executive summary of the FDA draft document). As is pointed out in the draft, relatively little Synercid is currently used in the U.S. Thus it is more realistic to attribute all streptogramin resistance observed in *Enterococcus faecium* in people to virginiamycin use in animals. When the calculations are based on this 100% scenario, then currently in the U.S. about 70 people per year (range 20 to 120) with *Enterococcus faecium* blood stream infections have adverse outcomes as the result of streptogramin resistance that results from virginiamycin use in animals.

The current FDA risk assessment underestimates both the current and future risks

I believe the FDA risk assessment underestimates both the current and likely future risks of adverse outcomes from resistant *Enterococcus* infections by a large amount. The model seems to use as the basis for its calculations on *Enterococcus faecium* bacteraemia, those episodes occurring in intensive care units, or ICUs (about 300,000; Chapter 6 page 75). These figures however are based mainly on NISS data, with the latter based on IV catheter infections.

If total blood stream infections in the entire U.S. population are considered, rather than just the ICU population, the septicemia figure is likely to be about 4 times higher than what was used in the model. As an example of the magnitude of this potential error we can look at the CDC estimates for Blood Stream Infections (BSI's) just caused by central vein IV catheters. The CDC estimates these catheters alone cause 250,000 blood stream infections per year in the U.S. – a large percentage of which do not originate in the ICU's. While very common, IV catheters would only account for about one quarter of all blood stream infections (Diekma et al). Hence, at least 1 million blood stream infections per year in the U.S. per year is a more realistic basis for

calculations (of which *Enterococcus faecium* presumably causes about 3% or 30,000 episodes). In short, the basis for parts of the FDA modeling in their risk assessment are problematic and will underestimate the current number of people in the U.S. that have adverse outcome as the result of streptogramin resistance in *Enterococcus faecium.*

A second source of underestimation will occur whenever discharge summary codes are used to derive BSI estimates. These codes often grossly underestimate the numbers of bloodstream infections that occur. Laboratory-based surveillance with a known and fully captured population base is the most accurate way to determine how frequent BSI's occur.

It is also important to note the comment in a recent review (Karchmer 2000 based on Edmond et al, 1999) that examined health-care related bloodstream infections "...vancomycin-resistant enterococci caused bacteremia more often in ward patients than in those in intensive care units". In my view this is likely to also be the case for streptogramin resistant *Enterococcus faecium.* In addition most vancomycin-resistant enterococci infections in health-care facilities in the US are clonal in origin, but the model thus not take into account this likely "clonal spread" scenario for streptogramin resistant *Enterococcus faecium*.

BSI's are the "tip of the iceberg" and thus many other serious infections are ignored in the FDA model

It is important to also realize that BSI's are the "tip of the iceberg" in terms of serious infections. The FDA model seems only to look at septicemia, ignoring more common (although typically less fatal) *Enterococcus faecium* infections –e.g. deep-seated surgical site infections, urinary tract, lung, surgical site infections etc) – that can be associated with significant morbidity, especially if no antibiotic was likely to be effective against the causative bacteria. For every blood stream infection, there are likely to be 5 times this number of serious deep-seated infections (eg joint, abdominal or lung infections) caused by invasive bacteria such as *Enterococcus faecium*. If we assume that there are 1,000,000 blood stream infections per year in the U.S. and that 11% are due to *Enterococcus spp* (see Diekema et al, J Clin Micro 2003) and that 25% of these are due to *Enterococcus faecium*, then this means there are about 30,000 blood-stream infections per year in the U.S. with *Enterococcus faecium* (1,000,000 x 0.11 x 0.25). Thus there will likely be 150,000 people (5 x 30,000) with serious *Enterococcus faecium* infections per year in the US.

The FDA virginiamycin risk assessment model does not take into account likely future scenarios

The FDA virginiamycin risk assessment model also does not take into account likely scenarios that will occur over the next 5 to 10 years and thus underestimates the likely harm that will result to people by the continued high volumes use of virginiamycin as an in feed additive for animals. This is a major problem with these FDA calculations as they are made on the basis of the current very low consumption of Synercid by people. This may not be true in 5 to 10 years time especially when we consider how common VRE (vancomycin resistant Enterococci) are now in U.S health-care facilities. We are likely to have much higher levels of VRE in health-care facilities and then there may be no alternative but to use streptogramins in many more people. However in 5 years time we are very likely have an even bigger population of resistant bacteria to streptogramins in foods and the environment.

It is also not reasonable to assume that the only patients who will benefits from or need streptogramins therapy are those with VRE isolates. The risk calculations should be done on the population that have any *Enterococcus faecium* infectors not just those that are also vancomycin resistant, which appears to be the basis of the current calculations.

Some modeling should also be done with the assumption that streptogramin use likely will increase because new and better streptogramin agents have been developed and released (or in the case that there is no choice but to use Synercid). The use of streptogramins may then equal current vancomycin use (i.e. a streptogramin replaces vancomycin because of widespread resistance to vancomycin). Modeling should thus also be done assuming that in the future that streptogramin use will need to be the same as the current use of vancomycin.

Other important models are ignored.

I am surprised that the FDA model did not reference or appear to use techniques similar to those already published that examined a number of different possible scenarios (including likely future scenarios - Smith et al, *Lancet Infectious Dis* 2003). In most of the modeling scenarios used by Smith et al, the use of virginiamycin was likely to be a significant contributor to either the level of streptogramin resistance seen in *Enterococcus faecium* or else virginiamycin use in animals contributed significantly to much high levels of resistance occurring in people at a much earlier time than would otherwise have occurred if streptogramins had been used in people alone.

FDA assessment does not do a society risk versus society benefits evaluation.

Another problem with the FDA assessment is that it does not do a society risk versus society benefits evaluation. If virginiamycin was shown to be effective and without it large mortality rates occur in poultry (eg 10% of poultry died instead of current rate of about 2%), then it is plausible that society may accept that up to 120 people per year in the U.S. may have a bad outcome (re the current upper limit on the risk calculation by the FDA). However as far as I can see if virginiamycin is used the way it is now (widespread as an in-feed additive) there are no medium to long term benefits that can be seen for animals by suitable experiments (the Pfizer studies in the 1980's indeed show a **higher** mortality in poultry receiving virginiamycin (4.8% vs. 3.9% in controls) and a likely dose response curve - see page 115 of the JETACAR review in Australia). Hence there may be currently a low risk for people but with NO or negligible benefits to the vast majority of animals (or their owners). In my mind this means society should not allow the current use of this drug because the risk to people (even though small) are much higher than an almost non existent "benefit" to animals documented by field experiments especially compared to other ways of preventing disease (like clean sheds!). This effectively means in the U.S. that 120 people (or more) have their lives put at risk per year (or die) for no or minimal benefits to animals with the current use of virginiamycin.

An assessment of the risk per volume of antibiotic used in food animals.

I also think doing an assessment of the likely risk per volume of antibiotic used in animals is also important. If we accept for a moment that the current FDA risk assessment is correct, in Australia if we take the top of the FDA estimate range - we would have about 10 people per year have an adverse outcome (120 divided by 15 - our population is 20 million compared to 300 million in U.S.). Thus it works out that 30,000 kgs of virginiamycin used in Australia results in 10 poor outcomes with *Enterococcus faecium* bacteraemia per year (ie 1 poor outcome per 3,000 kg of virginiamycin used). What this means however is that if use was decreased to 1,000 kgs per year here that instead of 10 deaths per year then we would only have a 1 death every 3 years (a

97% reduction in death rates!). I can imagine that there are some circumstances where virginiamycin may help (eg farms with outbreaks of NE). If virginiamycin use was restricted to those situations where there was a high probability of a "significant benefit", then consumption of virginiamycin on farms should go down markedly (by over 95%). Then this should mean that the total number of people coming to "grief" because of streptogramin resistance should fall also proportionality but without significantly compromising farming outputs or animal welfare.

Conclusion

In summary I believe the current FDA risk assessment significantly underestimates the numbers of people in the U.S. that currently have an adverse outcome per year due *Enterococcus faecium* bacteraemia. More importantly the model fails to take into account likely changes that will occur over the next 5 to 10 years. The model is based on estimates of bacteraemia in the U.S. that are too low and also does not take into account that there are many other types of serious infection due to *Enterococcus faecium* in addition to bacteraemia (e.g. deep seated surgical site infections). There are likely to be around 30,000 episodes of *Enterococcus faecium* bacteraemia per year in the U.S. and likely 5 times this number of other serious infections. Many of these isolates will have needlessly streptogramin resistant resulting from the needless use of virginiamycin use in animals. The available evidence suggests a poor benefit to society and animals from the current use of virginiamycin. Thus even if the estimates are as low as about 100 poor outcomes (and many of these will be deaths) in the U.S. per year due to the current use of this virginiamycin, these are needless poor outcomes in people that that could be prevented by the FDA if more appropriate restrictions were placed on the use of virginiamycin than currently occurs.

References

Risk Assessment of Streptogramin Resistance in *Enterococcus faecium A*ttributable to the Use of Streptogramins in Animals *"Virginiamycin Risk Assessment"*. FDA Center for Veterinary Medicine. Draft for Comment, 23-Nov-04

Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol. 2003 Aug;41(8):3655-60.

Karchmer AW. Nosocomial bloodstream infections: organisms, risk factors, and implications. Clin Infect Dis. 2000 Sep;31 Suppl 4:S139-43.

Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis. 1999 Aug;29(2):239-44.

CDC. Guidelines for the Prevention of Intravascular Catheter-Related Infections. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5110a1.htm

Smith DL, Johnson JA, Harris AD, Furuno JP, Perencevich EN, Morris JG Jr. Assessing risks for a pre-emergent pathogen: virginiamycin use and the emergence of streptogramin resistance in Enterococcus faecium. Lancet Infect Dis. 2003 Apr;3(4):241-9.

JETACAR. The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans**.** Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR**).** Office of National Health and Medical Research. Australian government. Department of Health and Aging. 22/October/1999. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubs-jetacar.htm