Designing Future Clinical Trials in Acute Pancreatitis

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Overall disease-related mortality from an episode of acute pancreatitis is approximately 10\% [1]. There are no specific therapies for acute pancreatitis apart from prophylactic antibiotics [2] and endoscopic sphincterotomy [3] for severe gallstone-related disease. The failure of the recent multi-centre study of the platelet activating factor antagonist lexipafant to demonstrate a reduction in mortality compared to placebo [4] together with the lack of full publication of the subsequent dose-ranging study of lexipafant [5] has produced a climate of nihilism regarding the future prospects for specific therapies. Although positive findings for novel agents which ameliorate the course of experimental acute pancreatitis continue to be reported, the transition from laboratory to clinical practice is problematic [6–8]. Difficulties in translational research may be multi-factorial: drugs that effectively ameliorate experimental acute pancreatitis may be less effective when administered in human trials several hours or days after onset of disease, funding restrictions may limit enthusiasm for adequately powered clinical trials and finally, the selection of relevant inclusion criteria and end-points can be difficult. Contemporary scientific approaches may be utilised in an attempt to overcome some of these difficulties by categorising experimental acute pancreatitis studies into two broad categories: those which seek to find insight into the mechanisms of disease and those which seek to evaluate potential new pharmacological agents or other therapeutic strategies. Studies in the latter category should be adequately powered and should select end-points (such as reduction in mortality or lung injury) that are capable of extrapolation to subsequent clinical evaluations.

Past experience has shown that accurate definition of the study cohort is central to the interpretation of findings. Following induction of acinar cell injury there are temporal changes in serum inflammatory marker profiles [9] and in remote organ injury [10]. It is critical that the temporal course of these events is related to trial interventions. Thus, future trials need to record the time from onset of symptoms to intervention in addition to the more conventionally recorded delay between hospital admission and intervention. Categorisation of severity usually involves the use of multiple factor prognostic scores of which the APACHE II is probably the best validated and most widely used [11]. Selection of APACHE II cut-off points critically influences the study population. Selection of an APACHE II cut-off of 9 (48 h after admission) has a sensitivity of 75\% and a specificity of 92\% for the detection of severe attacks [11]. Correspondingly, selecting a lower cut-off for inclusion will increase the proportion of patients with mild disease. Including patients scoring APACHE 6 or 7 at recruitment may be valuable but as the
risk of death in this subgroup will be low, effect of intervention on mortality is unlikely to be a useful principal end-point. When low and high-risk patients are included in randomised controlled trials, stratified randomisation by low and high APACHE score is essential to avoid chance imbalances between treatment arms.

A pragmatic alternative for stratifying patients at the point of entry is the ‘use of High Dependency Unit (HDU)/Intensive Care Unit (ICU)’. The inherent limitation of this policy is that criteria for admission to HDU may vary between clinicians in the same hospital or between hospitals. Variation in HDU admission trends between hospitals can be accommodated by stratifying randomisation by centre. Serum markers of severity such as those based on assays of components of the trypsinogen activation pathway [12], serum cytokine profiles or on markers of the systemic inflammatory response [13], may be used in future trials but at present these are not widely available in clinical practice. Similarly, early detection of patients with pancreatic necrosis by the use of serum markers such as calcitonin precursor peptides [13, 14] may allow future trials to focus interventions on those patients with biologically more severe forms of the disease.

Current disease categorisation in acute pancreatitis allocates an end-of-clinical episode status as mild or severe. Although this categorisation has been invaluable, limitations in this biphasic system have emerged with clinical use. In practice, there is a continuous spectrum of disease severity but perhaps more importantly, the organ dysfunction criteria used to allocate severe disease may be present transiently in patients whose illness runs a mild course [10]. Thus, categorisation of disease severity using the Atlanta conference criteria may be relatively imprecise and prone to interpretation error. More precise and better-validated organ dysfunction scoring systems such as the logistic organ dysfunction score are available [15] but are generally applicable only to intensive care unit populations. The effect of an intervention on organ dysfunction score is thus an interesting end-point but may be limited by the relatively small proportion of patients in a typical acute pancreatitis hospital admission cohort with organ failure scores in excess of 1.

It then follows that another critical aspect of future trial design is the need for relevant and interpretable end-points: mortality is important but more work is necessary in developing patient outcomes. Possibilities include measures of permanent target organ damage, disability, quality of life, pain scores, category of intervention, surgery, in-patient stay and return to work. Demonstrating cost-effectiveness and reductions in the cost of care, if sapient of the complexities of acute pancreatitis and individual health-care systems may provide an important handle in the evaluation of novel treatments.

Consumer input to trial design is increasingly seen as important. Involvement of patients in trial design may provide important validation of end-points and valuable insight into planned interventions and care.

There is evidence of geographical variation in predominant aetiologies for acute pancreatitis – in Britain, gallstone aetiology predominates [16] but alcohol is the predominant aetiological agents in other series [17]. In addition to variations in clinical disease profiles, there are likely variations across health-care systems in infrastructure and in the availability of equipment and clinical expertise. These differences apart, clinical acute pancreatitis is a recognisable, discrete clinical entity. Keys to enhancing the evidence-base for the treatment of acute pancreatitis may be sought in collaborative studies. In particular, issues such as the use of prophylactic antibiotics, early endoscopic sphincterotomy and the role of early enteral nutrition although all supported by small randomised trials [18] are amenable to definitive resolution by adequately powered studies. Incorporation of contemporary health economics criteria together with more appropriate selection, exclusion, stratification and end-point design should provide a rational framework for future clinical trials in acute pancreatitis in the 21st century.
References


