Management of Paracetamol Overdose

Abstract

In the United Kingdom the most common drug taken in overdose is paracetamol, which is recognised as a major cause of acute liver failure. However death rates from acute liver failure have fallen due to the rapid availability and accessibility of the antidote, acetylcysteine or N-acetylcysteine otherwise known as NAC.

In this article the authors will critically evaluate the current literature surrounding the assessment and management of patients presenting with paracetamol overdose in order to improve their own clinical practise and promote best practice within their clinical team. This will include discussion of presentation, risk factors, treatment, complications and referral to specialist centres for transplant.

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Paracetamol or Acetaminophen, is the most common drug taken in overdose leading to increased morbidity and mortality (Sheen and Dillon et al, 2002), and is recognised as a major cause of acute liver failure in the United Kingdom (UK) (Craig and Bates et al, 2010). However, acute liver failure secondary to paracetamol overdose remains rare in the UK, outside of specialist centres (Bernal, 2003). The low rate of deaths from paracetamol overdose appears to be associated with rapid availability and accessibility of the antidote, acetylcysteine or N-acetylcysteine otherwise known as NAC, used for paracetamol overdose since the 1970s (Bateman and Carroll et al, 2014). Paracetamol overdose accounts for approximately 40% of acute liver failure in the UK, however this figure has fallen since legislation was introduced in 1998 to limit the sale of paracetamol quantity sold over the counter (Bernal, 2002).

Acute liver Failure

Acute liver failure results from sudden extensive loss of liver cell mass resulting in hepatic encephalopathy and coagulopathy, leading to multi organ failure and a high mortality rate (Craig and Bates, 2010). Usually a therapeutic dose of paracetamol undergoes hepatic sulfation and glucuronidation resulting in excretion of non-toxic metabolites in the urine (Heard and Newton, 2018). However, approximately four per cent of paracetamol is metabolised by cytochrome P450 enzymes into N-acetyl-p-benzoquinone imine (NAPQI), a potentially toxic metabolite. Usually this combines

with intracellular glutathione to become a non-toxic mercapturate derivative and is excreted in the urine (Heard and Newton, 2018). However, in paracetamol overdose the production of NAPQI exceeds the capacity to detoxify it, binding to cellular components which cause mitochondrial injury and ultimately hepatocyte death (Heard and Newton, 2018).

Kalsi and Dargan et al (2011) argue that based on their review of the literature a link exists between low baseline intrahepatic glutathione in those with conditions such as human immunodeficiency virus (HIV), chronic hepatitis C infection, cystic fibrosis, malnutrition and eating disorders and increased risk of hepatotoxicity following paracetamol overdose. However, the authors acknowledge that published literature to date does not always recognise this association (Kalsi and Dargan et al, 2011). However, this is supported by Ferner et al (2011) who recognise this association and cite long term treatments with enzyme inducing drugs such as carbamazepine and phenytoin as high risk factors for hepatotoxicity.

The United States (US) Acute Liver Failure Study group reported that unintentional paracetamol overdose was the most common cause of acute liver failure caused by paracetamol overdose with 48% of overdoses (Larson and Polson et al, 2005). This contrasts with the reported pattern of overdose in the UK (Bernal, 2002). Earlier UK studies reported a significantly higher rate of acute liver failure in those who took an intentional overdose with suicidal intent (Makin et al, 1995). However, this has now been refuted by more recent UK research. Craig and Bates et al (2010) in their retrospective study of 938 patients found that unintentional paracetamol overdose is associated with a higher mortality rate than intentional paracetamol overdose.

Signs and symptoms of Paracetamol overdose

In both patterns of paracetamol ingestion causes for the overdose appear to be multifactorial including depression, poor packaging labelling, ingestion of multiple paracetamol containing medications, narcotic and alcohol misuse (Larson and Polson, 2005). Patients may present to the emergency department with no symptoms at all if within a few hours of ingestion of the paracetamol (Ferner et al, 2011). However, those who present more than 24 hours after ingestion may be exhibiting signs and symptoms of liver failure such as right upper quadrant tenderness, jaundice, asterixis, haemorrhage and impaired consciousness (Ferner et al, 2011). Furthermore,

ingestion of large quantities of paracetamol can lead to lactic acidosis and coma soon after presentation and later once hepatic failure is established (Shah et al, 2010). However, severe metabolic acidosis and hyperlactataemia may feature in very early severe paracetamol overdoses with only minimal elevations in transaminases and minimal coagulopathy reported (European Association for the Study of Liver (EASL), 2017). Staggered paracetamol overdoses may present with smaller elevations in serum transaminases but more pronounced organ failure (EASL, 2017).

Consideration of treatment

Hepatotoxicity is calculated from the blood concentration of paracetamol, and hours since ingestion (Buckley et al, 2016). Following a single episode of paracetamol ingestion, a paracetamol level should be checked four hours after ingestion and this level plotted against the time since ingestion on the treatment nomogram (Heard and Newton, 2018). Treatment should be considered if the paracetamol concentration level is above the treatment line on the nomogram as the risk of hepatotoxicity is low until significantly above this line (Buckley et al, 2016). However, the treatment nomogram is not useful in staggered overdoses and late presentations and therefore, in these cases, urgent commencement of treatment is recommended (Buckley et al, 2016). Furthermore, empirical treatment should be commenced if the patient is unconscious and paracetamol toxicity suspected, evidence of jaundice or hepatic tenderness, presentation more than eight hours after ingestion or uncertainty over the time of ingestion (Heard and Newton, 2018).

Calculating total dose of paracetamol ingested can be underestimated in the obese patient and therefore the National Institute of Health and Care Excellence (NICE) (2019) recommend using a standard weight of 110kg when calculating the total dose of paracetamol ingested for those patients who weigh more than 110kg. This ensures that these patients are not undertreated.

Reduction in paracetamol pack sizes

Measures such as reducing pack sizes were introduced in the UK in 1998 resulting in a reduction in large quantity paracetamol overdoses, liver transplants and deaths in England and Wales (Park et al, 2015). However, reductions in mortality in Scotland were only temporary, the reasons for which remain unclear (Park et al, 2015). The evidence suggests that the 1998 legislation has had long term benefits in reducing

paracetamol poisoning deaths (Hawton et al, 2013). However, there remains a substantial number of deaths annually from paracetamol poisoning and therefore further preventative measures may be required such as further reduction of pack sizes or reduction in paracetamol concentration (Hawton et al, 2013).

Treatment

Intravenous (IV) acetylcysteine is the antidote of choice used worldwide as it is almost 100% effective in preventing liver damage when administered within eight hours of ingestion according to the Medicines and Healthcare products Regulatory Agency (MHRA) (2014). Acetylcysteine restores hepatic glutathione therefore preventing hepatic injury (Heard, 2008). Treatment with IV acetylcysteine involves administering three infusions of acetylcysteine mixed with either five per cent dextrose or 0.9 per cent sodium chloride over 21 hours (Bailey and Najafi et al, 2016). The first infusion 150mg/kg is administered over one hour, the second bag 50mg/kg over four hours and 100mg/kg over 16 hours (Buckley et al, 2016). Acetylcysteine weight-based dosing regimens have been static for many years. However, Marks and Dargan et al (2016) argue that current acetylcysteine dosing does not consider other factors such as the amount of paracetamol taken, plasma paracetamol concentration, time to presentation and ingestion of other drugs. Furthermore, the authors highlight the lack of research in this area and therefore the real possibility that these patients may be undertreated (Marks and Dargan et al, 2016).

Acetylcysteine infusions are usually commenced in the emergency department and should run concurrently without delay to minimise treatment duration and length of stay whilst also maximising hepatic protection (Bailey and Najafi et al, 2016). However, Au and Zakaria (2014) argue that acetylcysteine administration is prone to error due to the complexity involved in calculating three different infusion concentrations and rates. Bailey and Najafi et al (2016) concluded in their UK study that delays in acetylcysteine treatment can lead to subtherapeutic plasma acetylcysteine levels and potentially avoidable hepatotoxicity. Buckley et al (2016) argue that if paracetamol concentration and liver function tests (LFTs) remain elevated despite completion of the course of acetylcysteine in patients showing signs of liver damage and those with large overdoses then further treatment with acetylcysteine of 150mg/kg per day should continue until there is evidence of significant improvement.

A systematic review which evaluated paracetamol overdose treatment in 11 randomised control trials found that activated charcoal was the best treatment to reduce absorption of the paracetamol and IV acetylcysteine to reduce the risk of toxicity therefore decreasing morbidity and mortality (Chiew and Gluud et al, 2018). The use of activated charcoal is usually confined to the emergency department. However, the Cochrane review acknowledged the distinct lack of evidence in comparing different treatment regimens and high risk of bias in all studies reviewed (Chiew and Gluud et al, 2018). Therefore, further high quality non- biased randomised control trials comparing treatment regimens are needed in this area.

Hypersensitivity and anaphylaxis

There is a risk of hypersensitivity and anaphylactic reactions with intravenous acetylcysteine treatment particularly in high risk groups, those with paracetamol concentrations below the treatment lines and in late presenters (Lynch and Robertson, 2004). However, guidance from the MHRA (2014) suggests that since these reactions are likely to be anaphylactoid and therefore not immunologically mediated then they may not reoccur on repeated exposure. Therefore, the MHRA (2014) argue that the benefits outweigh the risks in paracetamol overdose and consequently previous hypersensitivity should not be a contraindication to treatment with IV acetylcysteine. Unfortunately, these adverse drug reactions can lead to treatment interruptions and delays (Bateman and Dear et al, 2014). Bateman and Dear et al (2014) argue that a modified 12-hour treatment regime rather than the UK 21-hour standard regime is associated with less side effects such as nausea and a reduction in anaphylactic reactions. However, it appears that further randomised control trials are required to further evaluate this shorter regime as it has yet to be adopted in the UK.

Following a review by the Commission on Human Medicines of the treatment of paracetamol poisoning further recommendations were made such as increasing treatment of the first dose of acetylcysteine to over one hour rather than fifteen minutes to minimise the risk of adverse drug reactions (MHRA, 2014). However, Bateman and Carroll et al (2014) argue that their study shows no reduction in adverse drug effects with the increase in infusion time from 15 minutes to one hour. Furthermore, the authors of this study report an increased number of patients treated with acetylcysteine due to the lower treatment threshold implemented by the MHRA in 2012 resulting in a

higher number of patients at risk of anaphylaxis from acetylcysteine treatment (Bateman and Carroll et al, 2014). In addition, Gosselin et al (2013) argue that increased numbers of patients treated with acetylcysteine has led to increased secondary care costs. Further evaluation of the cost effectiveness of these recommendations in comparison to reduction in hepatotoxicity is needed.

Larson and Polson et al (2005) argue that the effects of both intentional and unintentional paracetamol overdose are essentially the same when the stage of acute liver failure has been reached. Complications associated with acute liver failure are varied and dependent on several variables such as pre-morbid state and age. Complications such as coagulopathy, poor nutritional status, sepsis, hepatic encephalopathy and renal failure may present with paracetamol induced liver failure (O'Grady, 2005).

Clinically, paracetamol overdose in large quantities or refractory to treatment, progress to hepatic encephalopathy through stages one to four in a few hours culminating in multi organ failure (EASL, 2017). The European guidelines for the management of acute liver failure suggest that those who do meet the criteria for liver transplant may still have a survival rate of 20-40% with modern intensive care management (EASL, 2017).

Prognostic scoring systems

O'Grady et al., developed the Kings College criteria in 1989 which identified which patients with paracetamol and non-paracetamol induced liver failure have a poor prognosis with medical management alone and would therefore benefit from liver transplant. Two meta-analyses evaluated the Kings College Criteria reporting 58-69% sensitivity and specificity of 92-94% in determining appropriate patients to be referred for transplantation (Craig et al, 2010, Bailey et al, 2003). Other prognostic criteria do exist, but evidence suggests these are less accurate than the Kings College criteria and therefore not widely used (Bailey et al, 2003). However, Bernal and Donaldson et al (2002) argue that although the Kings College criteria are widely utilised the addition of lactate level could facilitate earlier identification of those patients at highest risk of death from acute liver failure and therefore in most urgent need of liver transplantation (Bernal and Donaldson et al, 2002). Furthermore, Shah et al (2010) argue that lactic acidosis can be a marker of severity since the elevated lactate level reflects

mitochondrial inhibition by NAPQI. Although not included in the Kings College criteria, hyperlactaemia and hyperphosphataemia are considered strong predictors of poor prognosis without transplantation (Shah et al, 2010). Renner (2007) argues that future scoring systems should include both phosphate and lactate in addition to survival after transplantation in order to predict benefit of transplant in patients with acute liver failure.

Liver transplantation

Acute liver failure accounts for eight per cent of liver transplants in Europe (Adam et al, 2013). Patients in acute liver failure are prioritised on the transplant list despite the underlying aetiology of the acute liver failure with 45-50% of these patients undergoing transplantation (O'Grady, 2005). However, 25% appear to have contraindications to transplant and the remainder deteriorate before a transplant becomes available (O'Grady, 2005). In a multinational, multicentre, seven country study of acute liver failure transplantation, Gulmez and Larrey et al (2015) found that one sixth of all acute liver failure transplants were attributable to paracetamol overdose. However, there was variation in the rate of paracetamol overdose across Europe with this being higher in the UK and Ireland (Gulmez and Larrey et al, 2015). The differences and reasons for this are uncertain and therefore require further investigation.

In comparison to other groups, paracetamol overdose liver transplant is associated with poorer outcomes and higher mortality rate which Khan et al (2009) argue is likely related to the critical condition of these patients. Furthermore, the authors argue that these patients are usually critically unwell, likely on a ventilator in intensive care or encephalopathic and therefore have a poor pre-operative status which increases their risk of mortality. In addition, Khan et al (2009) also suggest that mortality is increased since these patients are listed for an urgent liver transplant and therefore, often receive the first available liver which may not be the best quality. Therefore, the combination of a critically unwell patient and a suboptimal liver is likely to lead to more complications, poorer outcomes and increased mortality (Khan et al, 2009).

Multidisciplinary team working

Paracetamol overdose patients can pose many challenges which must be assessed by a multidisciplinary team of hepatologists, surgeons and psychiatrists for their suitability to liver transplant which should be instigated promptly if clinically indicated

(Khan et al, 2009). Cooper and Aldridge et al (2009) argue there are concerns that paracetamol overdose patients may have underlying psychological and/ or psychiatric issues that may adversely affect their outcome post liver transplantation despite full social support. Therefore, an urgent psychiatric assessment will need to be completed which can be complicated if the patient is on a ventilator or encephalopathic. Therefore, collateral history should be taken from relatives and carers if appropriate to do so (Grover and Sarkar, 2012). Grover and Sarkar (2012) argue that although active mental health issues such as psychosis, substance misuse and personality disorder are contraindications to liver transplant these are not absolute and should be considered in context of the whole patient. Furthermore, the authors argue that transplant teams are generally more accepting of patients in whom the paracetamol overdose was an impulsive act rather than due to a recurrent pattern of self-harming behaviour due to an underlying mental health disorder (Grover and Sarker, 2012).

In addition to consideration of psychological factors a full evaluation of psychosocial factors should be completed. This needs to consider issues such as personality type, quality of life, their ability to cope with the demands of post-transplant recovery and lifelong adherence to immunosuppression and adequate social and emotional support going forward (Grover and Sarkar, 2012). Therefore, after consideration of all these factors there is a risk that these patients may be denied life-saving transplantation based on persistent underlying mental health issues and unmanageable adherence in order to ration availability of organs for transplant (Cooper and Aldridge et al, 2009). This raises ethical issues; by denying patients potentially life-saving treatment would be in direct violation of the ethical principle of beneficence and the ethical code of conduct to which healthcare practitioners abide. However, Cooper and Aldridge et al (2009) argue that denial of transplant can be justified due to the shortage of organ donors and therefore limited availability of healthy organs for transplant.

Patients who are deemed to be high risk of transplant failure due to mental health issues, substance misuse, recurrent self-harm attempts and poor adherence to treatment are unlikely to be listed for transplant when patients without these issues are also waiting for a liver transplant. These factors are considered by the transplant team, are not taken likely and a decision will only be made after full clinical, psychological and psychosocial assessments have been undertaken and multidisciplinary discussions have been completed.

Conclusion

Paracetamol overdose can be challenging to manage since it can present at varying times, different concentrations and as a variety of symptoms. Assessment of the quantity taken, time since ingestion and whether a single ingestion or staggered overdose are all essential questions to ask on presentation. Clear guidelines do exist on administration of the antidote treatment and potential side effects to be mindful of. Unfortunately, despite treatment some patients develop acute liver failure which requires referral to a hepatologist, and often a specialist centre for consideration of liver transplant. However, liver transplant is not straightforward and requires a complex, thorough set of clinical, psychological and psychosocial assessments before patients can be considered for transplant. Unfortunately, difficult decisions do sometimes have to be made if patients are considered unsuitable for transplant. The best supportive medical care is then the only means of treatment for these patients.

References

Adam, R., Karam, V., Delvart, V., O'Grady, J., Mirza, D., Klempnauer, J., Castaing, D., Neuhaus, P., Jamieson, N., Salizonni, M. (2013) 'Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR)', ***Journal of Hepatology,*** 57(3), pp. 675-688. doi: 10.1016/j.jhep.2012.04.015.

Au, V. and Zakaria, M.I. (2014) 'A study on the medication errors in the administration of N-acetylcysteine for paracetamol overdose patients in Malaysia', ***Hong Kong Journal of Emergency Medicine,*** 21(6), pp. 361-367. https://doi.org/10.1177/102490791402100604

Bailey, B., Amre, D.K. and Gaudreault, P. (2003) 'Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation', ***Critical Care Medicine,*** 31(1), pp. 299-305. doi:10.1097/00003246-200301000-00048

Bailey, G.P., Najafi, J., Elamin, M.E.M.O., Waring, W.S., Thomas, S.H.L., Archer, J.R.H., Wood, D.M. and Dargan, P.I. (2016) 'Delays during the administration of acetylcysteine for the treatment of paracetamol overdose', ***British Journal of Clinical Pharmacology,*** 82(5), pp. 1358-1363. https://doi.org/10.1111/bcp.13063

Bateman, D.N., Carroll, R., Pettie, J., Yamamoto, T., Elamin, M.E.M.O., Peart, L., Dow, M., Coyle, J., Cranfield, K.R., Hook, C., Sandilands, E.A., Veiraiah, A., Webb, D., Gray, A., Dargan, P.I., Wood, D.M., Thomas, S.H.L., Dear, J.W. and Eddleston, M. (2014) 'Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment', ***British Journal of Clinical Pharmacology,*** 78(3), pp. 610-618. https://doi.org/10.1111/bcp.12362

Bateman, D.N., Dear, J.W., Thanacoody, H.K.R., Thomas, S.H.L., Eddleston, M., Sandilands, E.A., Coyle, J., Cooper, J.G., Rodriguez, A., Butcher, I., Lewis, S.C., Vliegenthart, B., Veiraiah, A., Webb, D.J. and Gray, A. (2014) 'Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial', ***The Lancet,*** 383(9918), pp. 697-704. https://doi.org/10.1016/S0140-6736(13)62062-0

Bernal, W. (2003) 'Changing Patterns of Causation and the use of Transplantation in the United Kingdom', ***Seminars in Liver Disease,*** 23(3), pp. 227-238. doi:10.1055/s-2003-42640

Bernal, W., Donaldson, N., Wyncoll, D. and Wendon, J. (2002) 'Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study', ***The Lancet,*** 359(9306), pp. 558-563. doi: https://doi.org/10.1016/S0140-6736(02)07743-7

Buckley, N.A., Dawson, A.H. and Isbister, G.K. (2016) 'Treatments for paracetamol poisoning', ***British Medical Journal (BMJ),*** 353, doi: https://doi.org/10.1136/bmj.i2579

Chiew, A.L., Gluud, C., Brok, J. and Buckley, N.A. (2018) Interventions for paracetamol (acetaminophen) overdose. Cochrane Database of Systematic Reviews. CD003328. https://doi.org/10.1002/14651858.CD003328.pub3

Cooper, S.C., Aldridge, R.C., Shah, T., Webb, K., Nightingale, P., Paris, S., Gunson, B.K., Mutimer, D.J. and Neuberger, J.M. (2009) 'Outcomes of liver transplantation for paracetamol (acetaminophen) induced hepatic failure', ***Liver Transplantation,*** 15(10), pp. 1351-1357. https://doi.org/10.1002/lt.21799

Craig, D.G., Bates, C.M., Davidson, J.S., Martin, K.G., Hayes, P.C. and Simpson, K.J. (2010) 'Overdose pattern and outcome in paracetamol induced acute severe hepatotoxicity', ***British Journal of Clinical Pharmacology,*** 71(2), pp. 273-282.

https://doi.org/10.1111/j.1365-2125.2010.03819.x

Craig, D.G., Ford, A.C., Hayes, P.C. and Simpson, K.J. (2010) 'Systematic review: prognostic tests of paracetamol-induced acute liver failure', ***Alimentary Pharmacology and Therapeutics,*** 31(10), pp. 1064-1076. https://doi.org/10.1111/j.1365-2036.2010.04279.x

European Association for the Study of the Liver, Wendon, J., Cordoba, J., Dhawan, A., Larson, F.S., Manns, M., Samuel, D., Simpson, K.J. and Yaron, I. (2017) 'EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure', ***Journal of Hepatology****,* 66(5), pp. 1047-1081. doi: 10.1016/j.jhep.2016.12.003.

Ferner, R.E., Dear, J.W. and Bateman, D.N. (2011) 'Management of paracetamol poisoning', ***British Medical Journal (BMJ),*** 342, doi: https://doi.org/10.1136/bmj.d2218

Gosselin, S., Hoffman, R.S., Juurlink, D.N., Whyte, I., Yarema, M. and Caro. J. (2013) 'Treating acetaminophen overdose: threshold, costs and uncertainties', ***Clinical Toxicology,*** 51(3), pp. 130-133. doi**:** 10.3109/15563650.2013.775292

Grover, S. and Sarkar, S. (2012) 'Liver transplant – Psychiatric and Psychosocial Aspects', ***Journal of Clinical and Experimental Hepatology,*** 2(4), pp. 382-392. doi: 10.1016/j.jceh.2012.08.003

Gulmez, S.E., Larrey, D., Pageaux, G.P., Bearnuau, J., Bissoli, F., Horsmans, Y., Thorburn, D., McCormick, P.A., Stricker, B., Toussi, M., Lignot-Maleyran, S., Micon, S., Hamoud, F., Lasselle, R., Jove, J., Blin, P. and Moore, N. (2015) 'Liver transplant associated with paracetamol overdose: results from the seven country SALT study', ***British Journal of Clinical Pharmacology,*** 80(3), pp. 599-606. **https://doi.org/10.1111/bcp.12635**

Hawton, K., Bergen, H., Simkin, S., Dodd, S., Pocock, P., Bernal, W., Gunnell, D. and Kapur, N. (2013) 'Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses', ***British Medical Journal (BMJ),*** 346, doi: https://doi.org/10.1136/bmj.f403

Heard, K.J. (2008) 'Acetylcysteine for Acetaminophen Poisoning', ***The New England Journal of Medicine,*** 359, pp. 285-293. doi: 10.1056/NEJMct0708278

Heard, K. and Newton, A. (2018) 'Paracetamol overdose', ***BMJ Best practice,*** Available at: https://bestpractice.bmj.com (Accessed: 9 May 2019).

Kalsi, S.S., Dargan, P.I., Waring, W.S. and Wood, D.M. (2011) 'A review of the evidence concerning hepatic glutathione depletion and susceptibility to hepatotoxicity after paracetamol overdose', ***Open Access Emergency Medicine,*** 3, pp. 87-96. doi: https://doi.org/10.2147/OAEM.S24963

Khan, L.R., Oniscu, G.C. and Powell, J.J. (2009) 'Long-term outcome following liver transplantation', ***Transplant International,*** 23, pp. 524-529. doi:10.1111/j.1432-2277.2009.01007.x

Larson, A.M., Polson, J., Fontana, R.J., Davern, T.J., Lalani, E., Hynan, L.S., Reisch, J.S., Schiodt, F.V., Ostapowicz, G., Shakil, A.O. and Lee, W.M. (2005) 'Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study', ***Hepatology,*** 42(6), pp. 1364-1372. https://doi.org/10.1002/hep.20948

Lynch, R. and Robertson, R. (2004) 'Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case-controlled study', ***Accident and Emergency Nursing,*** 12(1), pp. 10-15. https://doi.org/10.1016/j.aaen.2003.07.001

Makin A.J., Wendon, J. and Williams, R. (1995) 'A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993)', ***Gastroenterology,*** 109(6), pp. 1907–16.

Marks, D.J.B., Dargan, P.I., Archer, J.R.H., Davies, C.L., Dines, A.M., Wood, D.M. and Greene, S.L. (2016) 'Outcomes from massive paracetamol overdose: a retrospective observational study', ***British Journal of Clinical Pharmacology,*** 83(6), pp. 1263-1272. **https://doi-org.ezproxy.derby.ac.uk/10.1111/bcp.13214**

Medicines and Healthcare Products Regulatory Agency (MHRA) (2014) ***Treating paracetamol overdose with intravenous acetylcysteine: new guidance.*** Available at: http://www.gov.uk (Accessed: 5 May 2019).

National Institute for Health and Care Excellence (NICE) (2019) ***Poisoning, emergency treatment.*** Available at: https://bnf.nice.org.uk/treatment-summary/poisoning-emergency-treatment.html (Accessed: 10 May 2019).

O'Grady, J.G. (2005) 'Acute liver failure', ***Postgraduate Medical Journal,*** 81(953), pp. 148-154. http://dx.doi.org/10.1136/pgmj.2004.026005

O'Grady, J.G., Alexander, G.J.M., Hayllar, K.M. and Williams, R. (1989) 'Early indicators of prognosis in fulminant hepatic failure', ***Gastroenterology,*** 97(2), pp. 439-445. https://doi.org/10.1016/0016-5085(89)90081-4

Park, B.K., Dear, J.W. and Antoine, D.J. (2015) 'Paracetamol (acetaminophen) poisoning', ***BMJ Clinical Evidence,*** 10(2101). Available at: http://www.bestpractice.bmj.com (Accessed: 5 May 2019).

Renner, E.L. (2007) 'How to decide when to list a patient with acute liver failure for liver transplantation? Clichy or King's College Criteria, or something else?', ***Journal of Hepatology,*** 46, pp. 553-582. doi: 10.1016/j.jhep.2007.01.009

Shah, A.D., Wood, D.M. and Dargan, P.I. (2010) 'Understanding lactic acidosis in paracetamol (acetaminophen) poisoning', ***British Journal of Clinical Pharmacology,*** 71(1), pp. 20-28. **https://doi.org/10.1111/j.1365-2125.2010.03765.x**

Sheen, C.L., Dillon, J.F., Bateman, D.N., Simpson, K.J. and Macdonald, T.M. (2002) 'Paracetamol toxicity: epidemiology, prevention and costs to the healthcare system', ***QJM: An Internal Journal of Medicine,*** 95(9), pp. 609-619. https://doi.org/10.1093/qjmed/95.9.609