International Journal of Histology and Cytology ISSN 2756-3707 Vol.9 (1) pp. 001-003, March, 2022. Available online at www.internationalscholarsjournals.com © International Scholars Journals

Mini Review

Looking closely at metabolic pathways for antipsychotics and antidepressants: A role in adherence testing, pharmacokinetics and molecularly specific mass spectrometry imaging

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Received: 03-Jan-2022, Manuscript No. IJHC-22-54276; Editor assigned: 05-Jan-2022, Pre QC No. IJHC-22-54276; (PQ); Reviewed: 19-Jan-2022, QC No. IJHC-22-54276; Revised: 07-Mar-2022, Manuscript No. IJHC-22-54276 (R); Published: 15-Mar-2022.

ABSTRACT

Recent laboratory studies have led to the identification of novel metabolites of antipsychotics in urine. These metabolites have further been demonstrated to enhance the sensitivity of LC/MSMS analysis of both forensic and toxicology samples. Knowledge of these metabolites may also be useful in functional mass spectrometry imaging. Finally, these metabolites are not limited to urine but are also resident in plasma.

Keywords: Antipsychotics, Haloperidol, Glucuronide, Mass spectrometry imaging, Toxicology

INTRODUCTION

Molecularly specific imaging using mass spectrometry has advanced past the prototype stage into a useful technique for tissue specific imaging. Recently, enzyme specific imaging has been reported wherein mass spectrometry is focused on enzyme mediated metabolic reactions to spatially imaging subcellular levels of these enzymes. However, such imaging is critically dependent upon knowledge of the metabolic pathway mitigated by the enzyme of choice. One area of medicine that continues to surprise with unique metabolites is that of mental health where antipsychotics have demonstrated a prevalence of unreported metabolites; specifically in urine.

LITERATURE REVIEW

The metabolism of many drugs has been well documented [1]. Yet, many unique metabolic pathways remain to be determined. Molecularly specific imaging using mass with respect to antipsychotics, the analysis of urine samples post hydrolysis by betaglucuronidase enzymes can yield enhanced levels of both parent drug (e.g., haloperidol) and conjugated metabolites (eg., norquetiapine). In other cases, metabolites demonstrated to be minor constituents in plasma have turned out to be more prevalent in urine (e.g., aripiprazole/OPC 3373). These findings have utility in traditional drug monitoring for adherence. However, their impact on imaging in tissues samples by functional mass spectrometry could be significant [4]. For example, imaging of the spatial distribution of glucuronide conjugating enzymes within liver cells could be enhanced through the use of these unique substrates as the reporter groups for the mass spectrometer. Without knowledge of these metabolic products, research would be limited to the analysis of parent drug distribution which may or may not reflect metabolic activity within the tissue of choice.

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spectrometry has advanced past the prototype stage into a useful technique for tissue specific imaging [2,3]. Recently, enzyme specific imaging has been reported wherein mass spectrometry is focused on enzyme mediated metabolic reactions to spatially imaging subcellular levels of these enzymes [4]. However, such imaging is critically dependent upon knowledge of the metabolic pathway mitigated by the enzyme of choice. One area of medicine that continues to surprise with unique metabolites is that of mental health where both antipsychotics and antidepressants demonstrate a prevalence of unreported metabolites; specifically in urine [5-10]. Recent reports of unique metabolites in urine compared with plasma resident active pharmaceutical ingredients and their corresponding metabolites have afforded enhanced sensitivity in the analysis of antipsychotics in urine for routine screening of patient adherence [11,12].

DISCUSSION

Reporting the distribution of these unique metabolites may also be useful albeit within limits as glucuronide conjugates are reported to be unstable under normal source conditions for mass spectrometry [13]. It is fair to ask whether this type of information is restricted to antipsychotics or is it more widespread across classes of mental health drugs. Work in our laboratory has demonstrated (Table 1) that hydrolysis of urine samples from a variety of antidepressant patients shows that several of the expected drugs and metabolites can be enhanced from this type of sample preparation. Positive urine samples identified using a fully validated LC/MSMS method [14]. Were tested for the impact of hydrolysis. An enzyme solution was prepared by diluting IMCSzyme β-glucuronidase solution (IMCS, Irmo, SC) to 10,000 units/mL in 0.02 M sodium phosphate buffer, at pH 7.5. Samples (30 µL) were diluted 6 x six times with 120 µL of enzyme solution and 30 uL of a 1000 ng/mL internal standard solution consistent with the validated method. After dilution, samples were incubated

at 60°C for 60 minutes for hydrolysis and then extracted using a solid-phase extraction method. Ultimately, samples were diluted 10 x ten times in 300 µL of 10% methanol: 90% water prior to injection and LC-MS/MS analysis [14]. These data suggest that some of these drugs and their metabolites are glucuronidated in urine and hence are "hidden" from analysis and imaging. Hydrolysis releases these moieties from the conjugation and enhances their concentration for analysis and imaging. The impact of such research on analysis of antipsychotics is clearly reported in work by McIntire, et al. Where in the impact of hydrolysis is compared with results from a recent forensic paper from South Korea [15]. In that work, Kim, et al., reported that neglecting to take mental health medications resulting from legal convictions can result in prison time for the patients. Hence, false negative results have a significant impact on the patient. Their reported limits of quantitation were much higher than those reported in the earlier work. Thus, patients who might have been positive may have been reported negative because the authors didn't look for the more prevalent metabolites that were conjugates of glucuronide. It is noteworthy to mention that the relevance of glucuronidated metabolites is not restricted to urine. These metabolites are found in plasma in both animals and in humans [16,17]. Determined the haloperidol glucuronide concentration in plasma from patients known to be prescribed the drug for treatment of schizophrenia. It was determined that the concentration of haloperidol glucuronide exceeded that of haloperidol itself, and the reduced form of haloperidol in these patient's plasma samples. Reported the glucuronidation of quetiapine in both *in vitro* cell suspensions and in plasma from patients. Conjugation of these and other drug metabolites is important both in urine and in plasma [18,19] (Table 1).

Table 1. Impact of beta glucuronidase hydrolysis on several antidepressants and metabolites.

Drug or metabolite name	Pre-hydrolysis concentration (ng/mL)	Post-hydrolysis concentration (ng/mL)	% difference
Bupropion	67.4	70.9	5
Hydroxybupropion	29	287	891
Citalopram	131.5	172.3	31
N-Desmethylcitalopram	146	163.3	11.9
Venlafaxine	2055.8	2947.7	43
Desvenlafaxine	21382	31290	46
Sertraline	9.6	374.7	3797

CONCLUSION

Continued research into metabolites in urine has the potential to enhance both traditional analysis of mental health drugs, further refine the reported pharmacokinetics and possibly assist molecularly specific imaging using these 'new' metabolites as target molecules. In addition, hookworm eggs Infective. hatch in the soil, releasing larvae that mature into a form that can actively penetrate into the skin. People become infected with hookworm primarily by walking barefoot on the contaminated soil. There is no direct person-to-person transmission, because eggs passed in faeces need about 3 weeks to mature in the soil before they become

REFERENCES

1. Baselt RC Disposition of Toxic Drugs and Chemicals in Man, 11th edition, Biomedical Publications: Seal Beach, CA. 2017.
2. Kaya I, Michno W, Brinet D, Iacone Y, Zanni G, et al. (2017) Histology-compatible MALDI mass spectrometry based imaging of neuronal lipids for subsequent immunofluorescent staining. Analytical chem. 89: 4685-4694.
3. Ferguson CN, Fowler JW, Waxer JF, Gatti RA, Loo JA (2014) Mass spectrometry-based tissue imaging of small molecules. Adv Exp Med Biol. 806: 283-299.
4. Hamilton BR, Marshall DL, Casewell NR, Harrison RA, Blanksby SJ, et al. (2020) Mapping enzyme activity on tissue by functional mass spectrometry imaging. Angew Chem Int Ed Engl. 132: 3883-3886.
5. Strickland EC, Enders JR, McIntire GL (2019) Determination of the Relative Prevalence of Lurasidone Metabolites in Urine Using Untargeted HRMS, Spectroscopy. 17: 8-15
6. Enders JR, Reddy SG, Strickland EC, McIntire GL (2017) Identification of metabolites of brexpiprazole in human urine for use in monitoring patient compliance. Clini Mass Spectro. 6: 21-24.
7. McIntire GL, Morris A (2015) Methods of monitoring for adherence to aripiprazole therapy. United States patent US. 9: 170-264.
8. Cummings OT, Strickland EC, Enders JR, McIntire G (2018) Impact of β-glucuronidase mediated hydrolysis on Haldol urinalysis. J Anal Toxicol. 42: 214-219.
9. Strickland EC, Cummings OT, Morris AA, Clinkscales A, McIntire GL (2016) Quetiapine carboxylic acid and quetiapine sulfoxide prevalence in patient urine. J Anal Toxicol. 40: 687-693.
10. Dretchen KL, Millet R, McIntire GL, Golub HL (2013) Quantitative levels of aripiprazole and its metabolites in urine. J Pharm Clin Toxicol. 1: 1014.
11. Feng S, Enders JR, Cummings OT, Strickland EC, McIntire T, et al. (2020) A Dilute and Shoot LC–

MS/MS Method for Antipsychotics in Urine. J Anal Toxicol. 44: 331-338.

12. McIntire GL, Strickland EC, Feng S, Enders J, Cummings OT, et al. (2021) A Comment on the levels of antipsychotics and their metabolites in urine. J Anal Pharm Res. 98-100
13. Enders, JR, Hitchcock, JC, Park, C, Morris, AA, McIntire GL, (2013) A Quantitative Inspection of ESI Glucuronide Degradation, ASMS, Minneapolis, MN.
14. Feng S, Bridgewater B, Strickland EC, McIntire G (2020) A Rapid LC–MS-MS Method for the Quantitation of Antiepileptic Drugs in Urine. J Anal Toxicol. 44: 688-696.
15. Kim SY, Kim HS, Cheong JC, Kim JY (2020) LC–MS-MS Determination of 25 Antipsychotic Drugs and Metabolites in Urine for Medication Compliance Monitoring. J Anal Toxicol. 448: 784-796.
16. Someya T, Shibasaki M, Noguchi T, Takahashi S, Inaba T, et al. (1992) Haloperidol metabolism in psychiatric patients: importance of glucuronidation and carbonyl reduction. J Clin Psychopharmacol. 12: 169-174.
17. Sattar H, Jadoon SS, Yang N, Li S, Xu M, et al. (2020) Role of glucuronidation pathway in quetiapine metabolism: An *in vivo* drug–drug interaction study between quetiapine and probenecid. Saudi J Med Med Sci. 8: 196.
18. Asai A, Miyazawa T (2000) Occurrence of orally administered curcuminoid as glucuronide and glucuronide/sulfate conjugates in rat plasma. Life sciences. 67: 2785-2793.
19. Muzzio M, Huang Z, Hu SC, Johnson WD, McCormick DL, et al. (2012) Determination of resveratrol and its sulfate and glucuronide metabolites in plasma by LC–MS/MS and their pharmacokinetics in dogs. J Pharm Biomed Anal. 59:201-218.